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Stump

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(54) **BICYCLIC DIHYDROIMIDAZOLONE CGRP RECEPTOR ANTAGONISTS**

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A61K 31/541 (2006.01)

A61K 31/5377 (2006.01)

(52) **U.S. Cl.**

USPC **514/227.8**; 514/231.5; 514/255.05;
544/60; 544/139; 544/230; 544/405

(58) **Field of Classification Search**

USPC 544/60, 139, 230, 405
See application file for complete search history.

(56) **References Cited**

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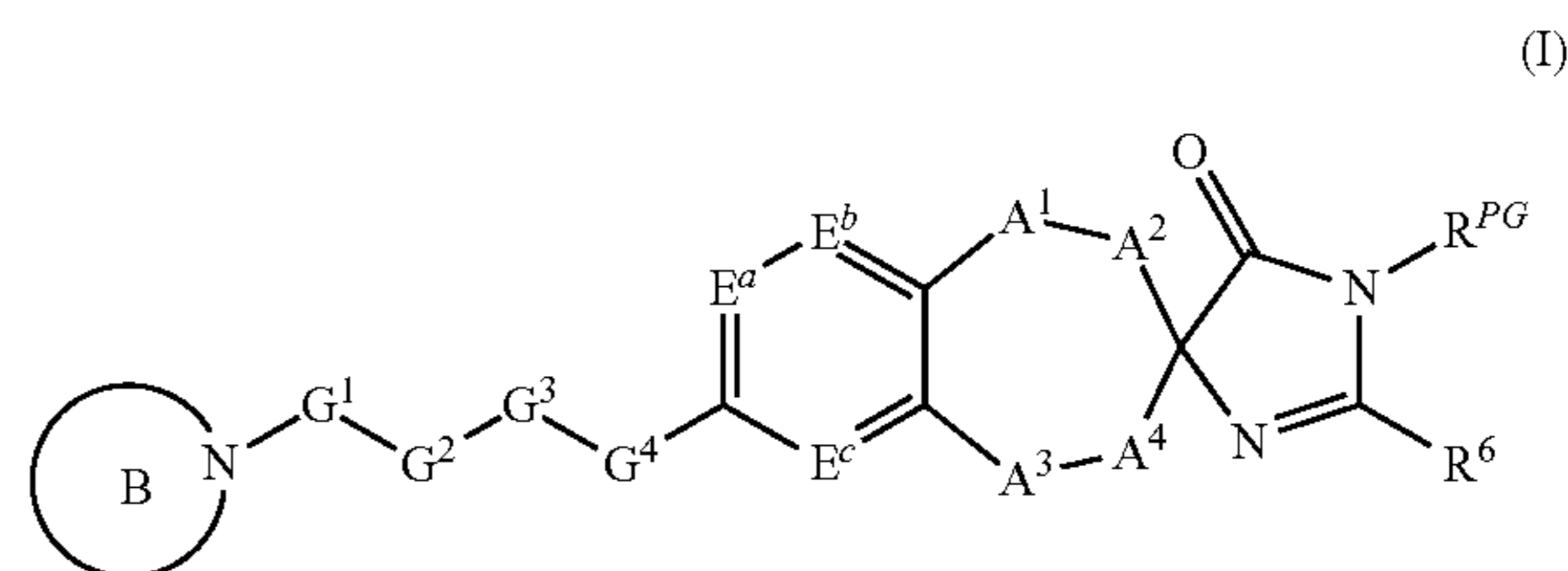
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(57) **ABSTRACT**

Compounds of formula (I): wherein variables B, G¹, G², G³, G⁴, E^a, E^b, E^c, A¹, A², A³, A⁴, R⁶ and R^{PG} and Y are as described herein, which are antagonists of CGRP receptors and which are useful in the treatment or prevention of diseases in which the CGRP is involved, such as migraine. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.



9 Claims, No Drawings

BICYCLIC DIHYDROIMIDAZOLONE CGRP RECEPTOR ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Phase application under 35 U.S.C. §371 of PCT Application No. PCT/US2009/056507 filed Sep. 10, 2009, which claims priority from U.S. Provisional Application Ser. No. 61/192,469, filed Sep. 18, 2008.

BACKGROUND OF THE INVENTION

CGRP (Calcitonin Gene-Related Peptide) is a naturally occurring 37-amino acid peptide that is generated by tissue-specific alternate processing of calcitonin messenger RNA and is widely distributed in the central and peripheral nervous system. CGRP is localized predominantly in sensory afferent and central neurons and mediates several biological actions, including vasodilation. CGRP is expressed in alpha- and beta-forms that vary by one and three amino acids in the rat and human, respectively. CGRP-alpha and CGRP-beta display similar biological properties. When released from the cell, CGRP initiates its biological responses by binding to specific cell surface receptors that are predominantly coupled to the activation of adenylyl cyclase. CGRP receptors have been identified and pharmacologically evaluated in several tissues and cells, including those of brain, cardiovascular, endothelial, and smooth muscle origin.

Based on pharmacological properties, these receptors are divided into at least two subtypes, denoted CGRP₁ and CGRP₂. Human α -CGRP-(8-37), a fragment of CGRP that lacks seven N-terminal amino acid residues, is a selective antagonist of CGRP₁, whereas the linear analogue of CGRP, diacetoamido methyl cysteine CGRP ([Cys(ACM)_{2,7}] CGRP), is a selective agonist of CGRP₂. CGRP is a potent neuromodulator that has been implicated in the pathology of cerebrovascular disorders such as migraine and cluster headache. In clinical studies, elevated levels of CGRP in the jugular vein were found to occur during migraine attacks (Goadsby et al., *Ann. Neurol.*, 1990, 28, 183-187), and salivary levels of CGRP were shown to be elevated in migraine subjects between attacks (Bellamy et al., *Headache*, 2006, 46, 24-33). CGRP itself has been shown to trigger migrainous headache (Lassen et al., *Cephalalgia*, 2002, 22, 54-61). In clinical trials, the CGRP antagonist BIBN4096BS has been shown to be effective in treating acute attacks of migraine (Olesen et al., *New Engl. J. Med.*, 2004, 350, 1104-1110) and was able to prevent headache induced by CGRP infusion in a control group (Petersen et al., *Clin. Pharmacol. Ther.*, 2005, 77, 202-213).

CGRP-mediated activation of the trigeminovascular system may play a key role in migraine pathogenesis. Additionally, CGRP activates receptors on the smooth muscle of intracranial vessels, leading to increased vasodilation, which is thought to contribute to headache pain during migraine attacks (Lance, *Headache Pathogenesis: Monoamines, Neuropeptides, Purines and Nitric Oxide*, Lippincott-Raven Publishers, 1997, 3-9). The middle meningeal artery, the principle artery in the dura mater, is innervated by sensory fibers from the trigeminal ganglion which contain several neuropeptides, including CGRP. Trigeminal ganglion stimulation in the cat resulted in increased levels of CGRP, and in humans, activation of the trigeminal system caused facial flushing and increased levels of CGRP in the external jugular vein (Goadsby et al., *Ann. Neurol.*, 1988, 23, 193-196). Electrical

stimulation of the dura mater in rats increased the diameter of the middle meningeal artery, an effect that was blocked by prior administration of CGRP(8-37), a peptide CGRP antagonist (Williamson et al., *Cephalalgia*, 1997, 17, 525-531).

5 Trigeminal ganglion stimulation increased facial blood flow in the rat, which was inhibited by CGRP(8-37) (Escott et al., *Brain Res.* 1995, 669, 93-99). Electrical stimulation of the trigeminal ganglion in marmoset produced an increase in facial blood flow that could be blocked by the non-peptide
10 CGRP antagonist BIBN4096BS (Doods et al., *Br. J. Pharmacol.*, 2000, 129, 420-423). Thus the vascular effects of CGRP may be attenuated, prevented or reversed by a CGRP antagonist.

CGRP-mediated vasodilation of rat middle meningeal
15 artery was shown to sensitize neurons of the trigeminal nucleus caudalis (Williamson et al., *The CGRP Family: Calcitonin Gene-Related Peptide (CGRP), Amylin, and Adrenomedullin*, Landes Bioscience, 2000, 245-247). Similarly, distention of dural blood vessels during migraine headache may sensitize trigeminal neurons. Some of the associated symptoms of migraine, including extra-cranial pain and facial allodynia, may be the result of sensitized trigeminal
20 neurons (Burstein et al., *Ann. Neurol.* 2000, 47, 614-624). A CGRP antagonist may be beneficial in attenuating, preventing or reversing the effects of neuronal sensitization.

The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans. Such disorders include
30 migraine and cluster headache (Doods, *Curr Opin Invest Drugs*, 2001, 2 (9), 1261-1268; Edvinsson et al., *Cephalalgia*, 1994, 14, 320-327); chronic tension type headache (Ashina et al., *Neurology*, 2000, 14, 1335-1340); pain (Yu et al., *Eur. J. Pharm.*, 1998, 347, 275-282); chronic pain (Hulsebosch et al., *Pain*, 2000, 86, 163-175); neurogenic inflammation and inflammatory pain (Holzer, *Neurosci.*, 1988, 24, 739-768; Delay-Goyet et al., *Acta Physiol. Scand.* 1992, 146, 537-538; Salmon et al., *Nature Neurosci.*, 2001, 4(4), 357-358); eye pain (May et al., *Cephalalgia*, 2002, 22, 195-196); tooth
40 pain (Awawdeh et al., *Int. Endocrin. J.*, 2002, 35, 30-36); non-insulin dependent diabetes mellitus (Molina et al., *Diabetes*, 1990, 39, 260-265); vascular disorders; inflammation (Zhang et al., *Pain*, 2001, 89, 265); arthritis, bronchial hyper-reactivity, asthma (Foster et al., *Ann. NY Acad. Sci.*, 1992, 657, 397-404; Schini et al., *Am. J. Physiol.*, 1994, 267, 112483-H2490; Zheng et al., *J. Virol.*, 1993, 67, 5786-5791); shock, sepsis (Beer et al., *Crit. Care Med.*, 2002, 30 (8), 1794-1798); opiate withdrawal syndrome (Salmon et al., *Nature Neurosci.*, 2001, 4(4), 357-358); morphine tolerance
50 (Menard et al., *J. Neurosci.*, 1996, 16 (7), 2342-2351); hot flashes in men and women (Chen et al., *Lancet*, 1993, 342, 49; Spetz et al., *J. Urology*, 2001, 166, 1720-1723); allergic dermatitis (Wallengren, *Contact Dermatitis*, 2000, 43 (3), 137-143); psoriasis; encephalitis, brain trauma, ischaemia, stroke, epilepsy, and neurodegenerative diseases (Rohrenbeck et al., *Neurobiol. of Disease* 1999, 6, 15-34); skin diseases (Gep-
55 petti and Holzer, Eds., *Neurogenic Inflammation*, 1996, CRC Press, Boca Raton, Fla.); neurogenic cutaneous redness, skin rosaceousness and erythema; tinnitus (Herzog et al., *J. Membrane Biology*, 2002, 189(3), 225); inflammatory bowel disease, irritable bowel syndrome, (Hoffman et al., *Scandinavian Journal of Gastroenterology*, 2002, 37(4) 414-422) and cystitis. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster
60 headache.

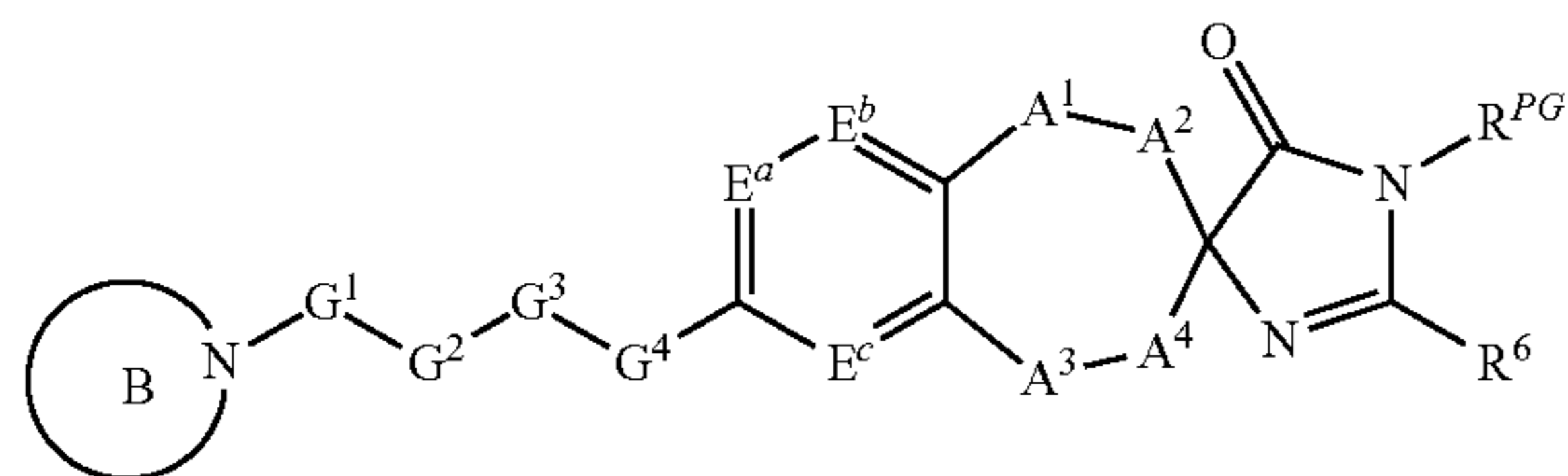
The present invention relates to compounds that are useful as ligands for CGRP receptors, in particular antagonists for

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CGRP receptors, processes for their preparation, their use in therapy, pharmaceutical compositions comprising them and methods of therapy using them.

SUMMARY OF THE INVENTION

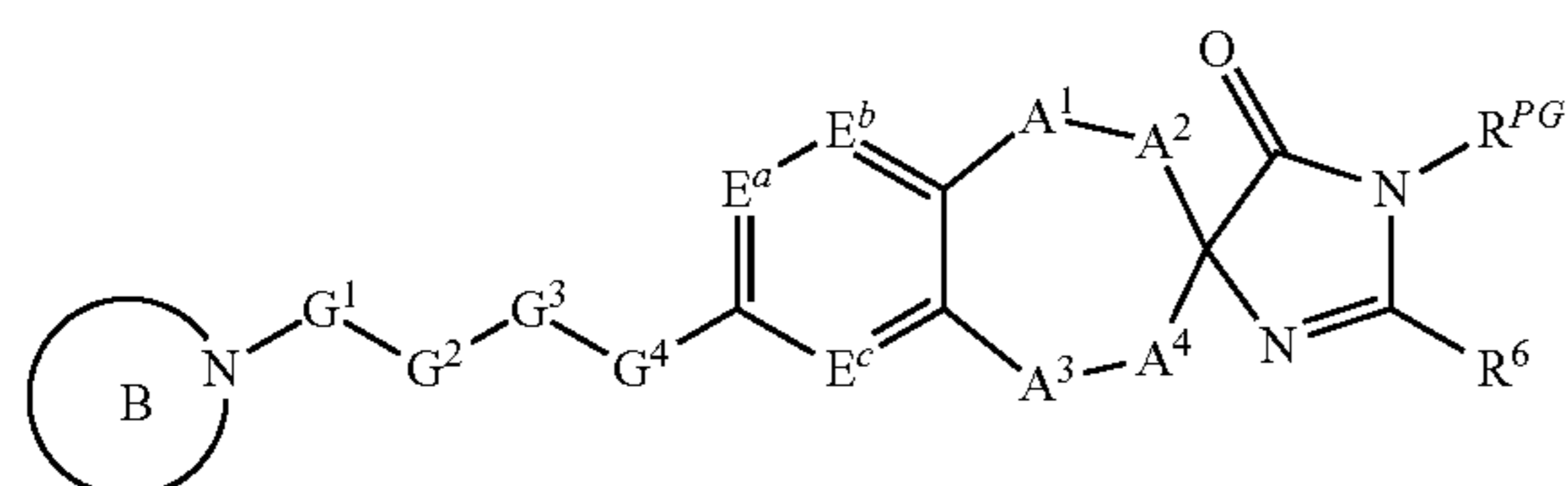
The present invention is directed to bicyclic dihydroimidazolone CGRP receptor antagonist compounds of formula I:



(wherein variables B, G¹, G², G³, G⁴, E^a, E^b, E^c, A¹, A², A³, A⁴, R⁶ and R^{PG} and Y are as described herein) which are antagonists of CGRP receptors and which are useful in the treatment or prevention of diseases in which CORP is involved, such as migraine The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.

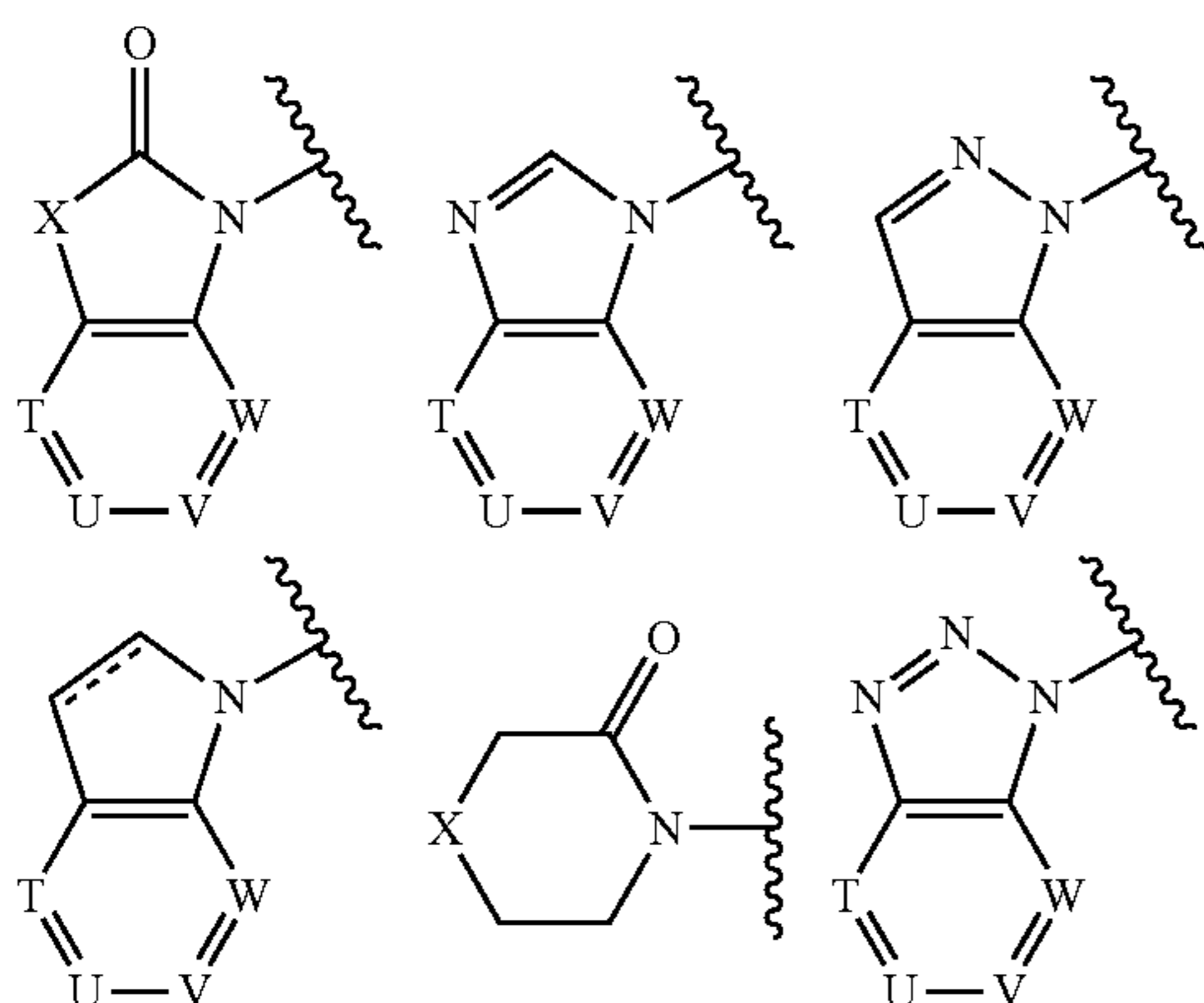
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to bicyclic dihydroimidazolone compounds of the formula I:



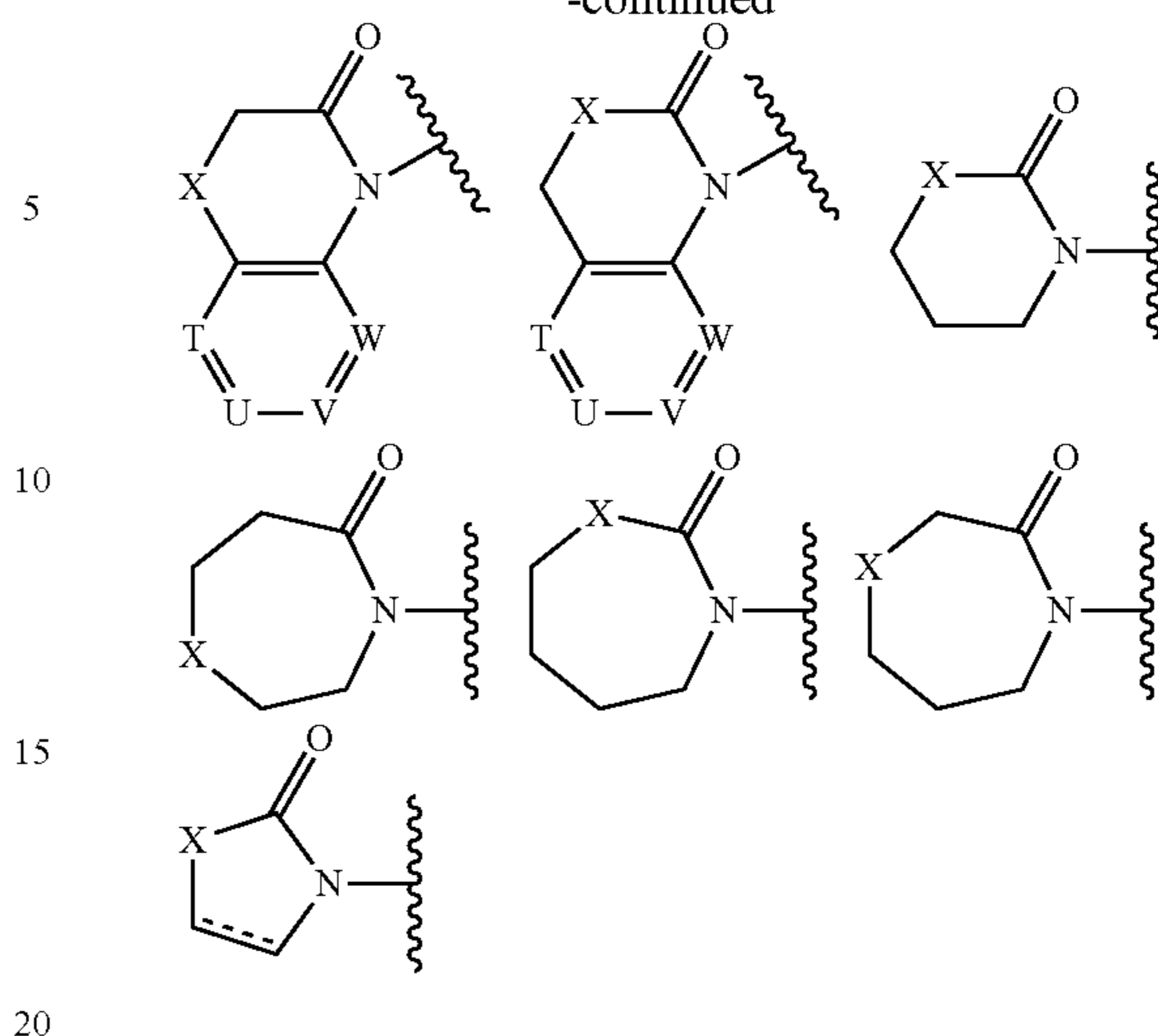
wherein:

B is a heterocycle selected from the group consisting of:



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-continued



wherein T, U, V, and W are each independently a carbon atom or a nitrogen atom, and no more than two of T, U, V and W are nitrogen atoms;

X is selected from:

- (1) —O—,
- (2) —S(O)_q—,
- (3) —Si(OR^a)—C₁₋₄alkyl-, where alkyl is unsubstituted or substituted with 1-5 halo,
- (4) —Si(C₁₋₄alkyl)₂, where each alkyl is independently unsubstituted or substituted with 1-5 halo-,
- (5) —N(R⁸)—,
- (6) —(C=O)—,
- (7) —C(R⁸)(R^a)—,
- (8) —C(N(R^b))—SO₂R^d(R^a)—,
- (9) —C(N(R^b))(C=O)R^a(R^a)—,
- (10) —C(N(R^b))(C=O)OR^a(R^a)—,
- (11) —CR¹⁰R¹¹—,
- (12) —N(R¹¹)—, and
- (13) —CR³R⁴—;

B is unsubstituted or substituted with 1-7 substituents each independently selected from R¹, R², R³, R⁴, R¹⁰, and R¹¹, wherein R¹, R², and R³ are independently selected from:

- (1) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 - (a) halo,
 - (b) hydroxy,
 - (c) —O—C₁₋₆alkyl,
 - (d) —C₃₋₆cycloalkyl,
 - (e) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, oxazolyl, thiazolyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from: —C₁₋₆alkyl, —O—C₁₋₆alkyl, halo, hydroxy, trifluoromethyl and —OCF₃,
 - (f) —CO₂R¹⁹,
 - (g) —NR²⁰R²¹,
 - (h) —SO₂R²²,
 - (i) —CONR^{20a}R^{21a},
 - (j) trifluoromethyl,
 - (k) —OCO₂R¹⁹,
 - (l) —(NR^{20a})CO₂R¹⁹,
 - (m) —O(CO)NR^{20a}R^{21a},
 - (n) —(NR¹⁹)(CO)NR^{20a}R^{21a}, and
 - (o) —O—C₃₋₆cycloalkyl,

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- (2) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
- halo,
 - hydroxy,
 - O—C₁₋₆alkyl,
 - trifluoromethyl,
 - phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: —C₁₋₆alkyl, —O—C₁₋₆alkyl, halo, hydroxy and trifluoromethyl,
- (3) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, thienyl, pyridazinyl, pyrrolidinyl, azetidiny, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, azepanyl, benzimidazolyl, benzopyranyl, benzofuryl, benzothiazolyl, benzoxazolyl, chromanyl, furyl, imidazoliny, indoliny, indolyl, quinoliny, isoquinoliny, tetrahydroquinoliny, isoindoliny, tetrahydroisoquinoliny, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, pyrazolidinyl, pyrazolyl, pyrrolyl, quinazoliny, tetrahydrofuryl, thiazoliny, puriny, naphthyridiny, quinoxaliny, 1,3-dioxolany, oxadiazolyl, piperidinyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiopyranyl, and morpholiny, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
- C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
 - halo,
 - hydroxy,
 - O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
 - C₃₋₆cycloalkyl,
 - phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, thienyl, or morpholiny, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from: —C₁₋₆alkyl, —O—C₁₋₆alkyl, halo, hydroxy and trifluoromethyl,
 - CO₂R¹⁹,
 - (CO)R¹⁹,
 - NR²⁰R²¹,
 - CONR²⁰R²¹,
 - oxo, and
 - S(O)_qR²²,
- halo,
 - oxo,
 - hydroxy,
 - O—C₁₋₆alkyl which is unsubstituted or substituted with 1-5 halo,
 - CN,
 - CO₂R¹⁹,
 - NR²⁰R²¹,
 - SO₂R²²,
 - CONR^{20a}R^{21a},
 - OCO₂R¹⁹,
 - (NR^{20a})CO₂R¹⁹,
 - O(CO)NR^{20a}R^{21a},
 - (NR¹⁹)(CO)NR^{20a}R^{21a},
 - (CO)—(CO)NR^{20a}R^{21a},
 - (CO)—(CO)OR¹⁹,
 - SO₂NR^{20a}R^{21a}, and
 - hydrogen;
- or R³ and R⁴ and the carbon atom to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, dioxolanyl, dioxanyl, aziridinyl, azetidiny, pyrrolidinyl, piperidi-

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nyl, piperazinyl, morpholiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiapyranyl, oxetanyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

- C₁₋₆alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
 - halo,
 - OR^a,
 - C₃₋₆cycloalkyl,
 - CO₂R^a,
 - NR^bR^c,
 - S(O)_qR^d,
 - C(=O)NR^bR^c, and
 - phenyl,
- phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholiny, thiazolyl and oxazolyl, wherein the phenyl or heterocycle is optionally fused to the ring, and which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - halo,
 - C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - OR^a,
 - CO₂R^a,
 - O(C=O)R^a,
 - CN,
 - NR^bR^c,
 - oxo,
 - C(=O)NR^bR^c,
 - N(R^b)C(=O)R^a,
 - N(R^b)CO₂R^a,
 - O(C=O)NR^bR^c, and
 - S(O)_qR^d,
- OR^a,
- halo,
- CO₂R^a,
- C(=O)NR^bR^c,
- S(O)_qR^d,
- CN,
- NR^bR^c,
- N(R^b)C(=O)R^a,
- N(R^b)SO₂R^d,
- O—CO₂R^d,
- O—(C=O)—NR^bR^c,
- NR^b—(C=O)—NR^bR^c,
- C(=O)R^a, and
- oxo;

A¹ and A³ are independently selected from:

- O—,
- S(O)_q—,
- Si(OR^a)(C₁₋₄alkyl)-, where alkyl is unsubstituted or substituted with halo,
- Si(C₁₋₄alkyl)₂-, where each alkyl is independently unsubstituted or substituted with 1-5 halo-,
- CR^eR^f—,
- N(R⁴)—,
- (C=O)—, and
- a bond;

A² and A⁴ are independently selected from:

- O—,
- S(O)_q—,

- (3) —Si(OR^a)(C₁₋₄alkyl)-, where alkyl is unsubstituted or substituted with halo,
 (4) —Si(C₁₋₄alkyl)₂-, where each alkyl is independently unsubstituted or substituted with 1-5 halo-,
 (5) —CR^eR^f—,
 (6) —N(R⁴)—, and
 (7) —(C=O)—;

E^a, E^b, and E^c are each independently selected from:

- (1) —C(R⁵)=,
 (2) —N=, and
 (3) —((N⁺—O)—)=;

G¹ is selected from:

- (1) a bond,
 (2) —CR^eR^f—,
 (3) —CR^eR^f—CH₂—,
 (4) —CH₂—CR^eR^f—, and
 (5) —(C=O)—;

G² is selected from:

- (1) a bond,
 (2) —CR^eR^f—,
 (3) —CR^eR^f—CH₂—,
 (4) —CH₂—CR^eR^f—,
 (5) —(C=O)—,
 (6) —N(R⁴)—,
 (7) —O—,
 (8) —S(O)_q—,
 (9) —SiR^gR^h—,
 (10) —C(Rⁱ)=C(R^j)—, and
 (11) —C≡C—;

G³ is selected from:

- (1) a bond,
 (2) —CR^eR^f—,
 (3) —N(R⁴)—,
 (4) —O—,
 (5) —S(O)_q—,
 (6) —SiR^gR^h—,
 (7) —C(Rⁱ)=C(R^j)—,
 (8) —C≡C—, and
 (9) —(C=O)—;

G⁴ is selected from:

- (1) —CR^eR^f—,
 (2) —N(R⁴)—,
 (3) —O—,
 (4) —S(O)_q—,
 (5) —SiR^gR^h—,
 (6) —C(Rⁱ)=C(R^j)—, and
 (7) —C≡C—;

R⁴ is independently selected from:

- (1) hydrogen,
 (2) —C(=O)R^a,
 (3) —CO₂R^a,
 (4) —S(=O)R^d,
 (5) —SO₂R^d,
 (6) —C(=O)NR^bR^c,
 (7) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) halo,
 (b) —OR^a,
 (c) —C₃₋₆cycloalkyl,
 (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (i) halo,
 (ii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 (iii) —OR^a,
 (iv) —NR^bR^c,
 (v) —C(=O)R^a,
 (vi) —CO₂R^a, and
 (vii) oxo;
 (e) —CO₂R^a,
 (f) —C(=O)NR^bR^c,
 (g) —S(O)_qR^d,
 (h) —CN,
 (i) —NR^bR^c,
 (j) —N(R^b)C(=O)R^a,
 (k) —N(R^b)SO₂R^d,
 (l) —CF₃,
 (m) —O—CO₂R^d,
 (n) —O—(C=O)—NR^bR^c,
 (o) —NR^b—(C=O)—NR^bR^c, and
 (p) —C(=O)R^a;
 (8) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 (a) halo,
 (b) —CN,
 (c) —OR^a, and
 (d) C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo;
 R⁵ is independently selected from:
 (1) hydrogen,
 (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 (a) halo,
 (b) hydroxy,
 (c) —OC₁₋₆alkyl,
 (d) —C₃₋₆cycloalkyl,
 (e) phenyl,
 (f) —CONR^{20a}R^{21a},
 (g) —CO₂R¹⁹, and
 (h) —NR²⁰R²¹,
 (3) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 fluoro,
 (4) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) —C₁₋₄alkyl, which is unsubstituted or substituted with 1-5 fluoro,
 (b) halo,
 (c) —CN,
 (d) hydroxy, and
 (e) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
 (5) halo,
 (6) hydroxy,
 (7) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 (8) —CN,
 (9) —CO₂R¹⁹,
 (10) —NR²⁰R²¹,
 (11) —SO₂R²²,
 (12) —CONR^{20a}R^{21a},
 (13) —OCO₂R¹⁹, and
 (14) —(NR^{20a})CO₂R¹⁹;

R⁶ is selected from:

- (1) hydrogen;
- (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 - (a) halo, 5
 - (b) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
 - (c) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 fluoro, and
 - (d) phenyl or heterocycle, wherein heterocycle is 10
 - selected from: azepinyl, azepanyl, azetidiny, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothioapyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, dibenzofuranyl, 15
 - dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothioapyranyl, dihydrobenzothioapyranyl sulfone, furyl, furanyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, morpholiny, 20
 - naphthyridiny, oxazolyl, oxadiazolyl, 2-oxoazepiny, 4-oxonaphthyridiny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxopyridyl, 2-oxoquinoliny, piperidyl, piperaziny, pyraziny, pyrazolidiny, pyrazolyl, pyridaziny, pyridiny, 25
 - pyridyl, pyrimidiny, pyrimidyl, pyrrolidiny, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridiny, tetrahydroisoquinoliny, 30
 - tetrahydroquinoliny, tetrazolyl, thiamorpholiny, thiamorpholiny sulfoxide, thiamorpholiny sulfone, thiazolyl, thiazoliny, thienofuryl, thienothienyl, thienyl, isoxazolyl, tetrahydrothienyl, tetrahydroapyranyl, oxetanyl, tetrahydrothiapyranyl, thietanyl, and triazolyl, which phenyl or heterocycle is unsubstituted or 35
 - substituted with 1-3 substituents each independently selected from: —C₁₋₆alkyl, —O—C₁₋₆alkyl, halo, hydroxy, trifluoromethyl, —CN, and —OCF₃,
 - (3) phenyl or heterocycle, wherein heterocycle is 40
 - selected from: azepinyl, azepanyl, azetidiny, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothioapyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothioapyranyl, dihydrobenzothioapyranyl sulfone, furyl, furanyl, imidazolidiny, imidazoliny, imidazolyl, indoliny, indolyl, isoindoliny, isoquinoliny, isothiazolidiny, isothiazolyl, morpholiny, naphthyridiny, oxazolyl, oxadiazolyl, 2-oxoazepiny, 4-oxonaphthyridiny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxopyridyl, 2-oxoquinoliny, piperidyl, piperaziny, pyraziny, pyrazolidiny, pyrazolyl, pyridaziny, pyridiny, pyridyl, pyrimidiny, pyrimidyl, pyrrolidiny, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridiny, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, thiamorpholiny, thiamorpholiny sulfoxide, thiamorpholiny sulfone, thiazolyl, thiazoliny, thienofuryl, thienothienyl, thienyl, 60
 - isoxazolyl, tetrahydrothienyl, tetrahydroapyranyl, oxetanyl, tetrahydrothiapyranyl, thietanyl, and triazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from: 65
 - (a) halo,
 - (b) —OR^a,

- (c) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 fluoro,
 - (d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (i) halo,
 - (ii) —CN,
 - (iii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo, and
 - (iv) —OR^a,
 - (e) —CO₂R^a,
 - (f) —C(=O)NR^bR^c,
 - (g) —S(O)_qR^d,
 - (h) —CN,
 - (i) —NR^bR^c,
 - (j) —N(R^b)C(=O)R^a,
 - (k) —N(R^b)SO₂R^d,
 - (l) —O—CO₂R^d,
 - (m) —O—(C=O)—NR^bR^c,
 - (n) —NR^b—(C=O)—NR^bR^c,
 - (o) —C(=O)R^a, and
 - (p) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
 - (4) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (5) —CN,
 - (6) —CO₂R¹⁹,
 - (7) —NR²⁰R²¹, and
 - (8) —CONR^{20a}R^{21a}
 - (9) —C₁₋₆cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) halo,
 - (b) —CN,
 - (c) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (d) —OR^a, and
 - (e) phenyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are each independently selected from:
 - (i) —OR^a,
 - (ii) halo,
 - (iii) —CN, and
 - (iv) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo;
- R⁸ is independently selected from:
- (1) hydrogen,
 - (2) —C(=O)R^a,
 - (3) —CO₂R^a,
 - (4) —S(=O)R^d,
 - (5) —SO₂R^d,
 - (6) —C(=O)NR^bR^c,
 - (7) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) halo,
 - (b) —OR^a,
 - (c) —C₃₋₆cycloalkyl,
 - (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidiny, pyraziny, pyridaziny, piperidiny, piperaziny, pyrrolidiny, thienyl, morpholiny, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (i) halo,
 - (ii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (iii) —OR^a,
 - (iv) —NR^bR^c,

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- (v) $-\text{C}(=\text{O})\text{R}^a$,
 (vi) $-\text{CO}_2\text{R}^a$,
 (vii) oxo, and
 (viii) $-\text{CN}$,
 (e) $-\text{CO}_2\text{R}^a$,
 (f) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$,
 (g) $-\text{S}(\text{O})_q\text{R}^d$,
 (h) $-\text{CN}$,
 (i) $-\text{NR}^b\text{R}^c$,
 (j) $-\text{N}(\text{R}^b)\text{C}(=\text{O})\text{R}^a$,
 (k) $-\text{N}(\text{R}^b)\text{SO}_2\text{R}^d$,
 (l) $-\text{CF}_3$,
 (m) $-\text{O}-\text{CO}_2\text{R}^d$,
 (n) $-\text{O}-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$,
 (o) $-\text{NR}^b-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$, and
 (p) $-\text{C}(=\text{O})\text{R}^a$,
 (8) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 (a) halo,
 (b) $-\text{CN}$,
 (c) $-\text{OR}^a$, and
 (d) C_{1-6} alkyl, which is unsubstituted or substituted with 1-6 halo;
 or R^4 and R^8 and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl- ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:
 (a) halo,
 (b) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a , CN , and $-\text{C}(=\text{O})\text{OR}^a$,
 (c) $-\text{OR}^a$, and
 (d) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo;
 R^{10} is independently selected from:
 (1) hydrogen,
 (2) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) halo,
 (b) $-\text{OR}^a$,
 (c) $-\text{CN}$,
 (d) phenyl, and
 (e) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 (3) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo;
 R^{11} is independently selected from the group consisting of:
 phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl, azepinyl, azepanyl, azetidiny, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, chromanyl, cinnoliny, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, furanyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, morpholiny, naphthyridinyl, oxazolyl, oxadiazolyl, 2-oxoazepinyl, 4-oxonaphthyridinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxopyridyl, 2-oxoquinoliny, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuranyl, tetrahydrofuryl, tetrahy-

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- droimidazopyridinyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, thiamorpholiny, thiamorpholiny sulfoxide, thiamorpholiny sulfone, thiazolyl, thiazoliny, thienofuryl, thienothienyl, thienyl, triazolyl, isoxazolyl, tetrahydrothienyl, tetrahydropyranyl, oxetanyl, tetrahydrothiopyranyl, and thietanyl, where R^{11} is unsubstituted or substituted with 1-5 substituents each independently selected from R^{12} , R^{13} , R^{14} , R^{15a} and R^{15b} ;
 R^{12} , R^{13} , R^{14} , R^{15a} and R^{15b} are each independently selected from:
 (1) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) halo,
 (b) $-\text{OR}^a$,
 (c) $-\text{C}_{3-6}$ cycloalkyl,
 (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholiny, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (i) halo,
 (ii) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo, and
 (iii) $-\text{OR}^a$,
 (e) $-\text{CO}_2\text{R}^a$,
 (f) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$,
 (g) $-\text{S}(\text{O})_q\text{R}^d$,
 (h) $-\text{CN}$,
 (i) $-\text{NR}^b\text{R}^c$,
 (j) $-\text{N}(\text{R}^b)\text{C}(=\text{O})\text{R}^a$,
 (k) $-\text{N}(\text{R}^b)\text{SO}_2\text{R}^d$,
 (l) $-\text{CF}_3$,
 (m) $-\text{O}-\text{CO}_2\text{R}^d$,
 (n) $-\text{O}-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$,
 (o) $-\text{NR}^b-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$, and
 (p) $-\text{C}(=\text{O})\text{R}^a$,
 (2) $-\text{C}_{1-6}$ cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) halo,
 (b) $-\text{CN}$,
 (c) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
 (d) $-\text{OR}^a$, and
 (e) phenyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are each independently selected from:
 (i) $-\text{OR}^a$,
 (ii) halo,
 (iii) $-\text{CN}$, and
 (iv) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
 (3) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperdinyl, piperazinyl, pyrrolidinyl, thienyl, morpholiny, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) halo,
 (b) $-\text{OR}^a$,
 (c) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 (d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

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- (i) halo,
(ii) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo, and
(iii) $-OR^a$,
(e) $-CO_2R^a$,
(f) $-C(=O)NR^bR^c$,
(g) $-S(O)_qR^d$,
(h) $-CN$,
(i) $-NR^bR^c$,
(j) $-N(R^b)C(=O)R^a$,
(k) $-N(R^b)SO_2R^d$,
(l) $-O-CO_2R^d$,
(m) $-O-(C=O)-NR^bR^c$,
(n) $-NR^b-(C=O)-NR^bR^c$,
(o) $-C(=O)R^a$, and
(p) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
- (4) halo,
(5) oxo,
(6) $-OR^a$,
(7) $-CN$,
(8) $-CO_2R^a$,
(9) $-C(=O)R^a$,
(10) $-NR^bR^c$,
(11) $-S(O)_qR^d$,
(12) $-C(=O)NR^bR^c$,
(13) $-O-CO_2R^d$,
(14) $-N(R^b)CO_2R^d$,
(15) $-O-(C=O)-NR^bR^c$,
(16) $-NR^b-(C=O)-NR^bR^c$,
(17) $-SO_2NR^bR^c$,
(18) $-N(R^b)SO_2R^d$,
or R^{15a} and R^{15b} and the atom(s) to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (a) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
(i) halo,
(ii) $-OR^a$,
(iii) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
(iv) $-CO_2R^a$,
(v) $-NR^bR^c$,
(vi) $-S(O)_qR^d$,
(vii) $-C(=O)NR^bR^c$, and
(viii) phenyl,
(b) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
(i) halo,
(ii) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo, and
(iii) $-OR^a$,
(c) $-OR^a$,
(d) halo,
(e) $-CO_2R^a$,
(f) $-C(=O)NR^bR^c$,

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- (g) $-S(O)_qR^d$,
(h) $-CN$,
(i) $-NR^bR^c$,
(j) $-N(R^b)C(=O)R^a$,
(k) $-N(R^b)SO_2R^d$,
(l) $-O-CO_2R^d$,
(m) $-O-(C=O)-NR^bR^c$,
(n) $-NR^b-(C=O)-NR^bR^c$, and
(o) $-C(=O)R^a$;
- R^{19} is independently selected from:
(1) hydrogen,
(2) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 substituents, each independently selected from:
(a) halo,
(b) hydroxy,
(c) $-OC_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
(d) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo, and
(e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
(i) $-C_{1-4}$ alkyl,
(ii) $-OC_{1-6}$ alkyl,
(iii) halo,
(iv) trifluoromethyl, and
(v) $-OCF_3$,
(3) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 substituents, substituents each independently selected from:
(a) halo,
(b) hydroxy,
(c) $-O-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
(d) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo, and
(e) phenyl,
(4) phenyl or heterocycle, wherein heterocycle is selected from: pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, pyrrolidinyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, imidazoliny, indolinyl, indolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, isoindolinyl, tetrahydroisoquinolinyl, tetrahydrofuryl, quinoxaliny, piperidinyl, piperazinyl, and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
(a) halo,
(b) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo
(c) $-OC_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo
(d) $-C_{3-6}$ cycloalkyl,
(e) oxo,
(f) $-CN$,
(g) hydroxy, and
(h) phenyl;
- R^{20} and R^{21} are each independently selected from:
(1) hydrogen,
(2) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
(a) halo,
(b) hydroxy,
(c) $-OCF_3$,
(d) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo, and
(e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

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- (i) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (ii) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (iii) —CN
 - (iv) halo, and
 - (v) trifluoromethyl,
 - (3) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 - (4) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (c) halo,
 - (d) hydroxy,
 - (e) trifluoromethyl,
 - (f) —OCF₃, and
 - (g) —CN,
 - (5) —COR¹⁹, and
 - (6) —SO₂R²²;
- R^{20a} and R^{21a} are each independently selected from:
- (1) hydrogen,
 - (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 - (a) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) halo,
 - (c) hydroxy,
 - (d) —OCF₃,
 - (e) —C₃₋₆cycloalkyl, and
 - (f) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (i) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (ii) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (iii) —CN
 - (iv) halo, and
 - (v) trifluoromethyl,
 - (3) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-5 halo,
 - (4) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (c) halo,
 - (d) hydroxy,
 - (e) trifluoromethyl,
 - (f) —OCF₃, and
 - (g) —CN,
- or where R^{20a} and R^{21a} join to form a ring selected from azetidiny, pyrrolidiny, piperidiny, azepany, piperaziny and morpholiny, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (1) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (2) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (3) halo
 - (4) hydroxy
 - (5) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

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- (a) —C₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo,
 - (b) —O—C₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo, and
 - (c) halo,
 - (6) benzyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo,
 - (b) —OC₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo, and
 - (c) halo,
 - (7) —COR¹⁹, and
 - (8) —SO₂R²²;
- R²² is selected from:
- (1) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
 - (2) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-5 halo,
 - (3) phenyl or heterocycle, wherein heterocycle is selected from: pyridiny, pyrimidiny, pyraziny, pyridaziny, piperidiny, piperaziny, pyrrolidiny, thieny and morpholiny, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (c) halo,
 - (d) hydroxy,
 - (e) trifluoromethyl,
 - (f) —OCF₃,
 - (g) —CN, and
 - (h) benzyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (i) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (ii) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (iii) halo, and
 - (iv) trifluoromethyl;
- R^{PG} is selected from:
- (1) hydrogen,
 - (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 - (a) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) halo,
 - (c) hydroxy,
 - (d) —OCF₃,
 - (e) —C₃₋₆cycloalkyl, and
 - (f) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (i) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
 - (ii) —OR^a,
 - (iii) —CN
 - (iii) halo, and
 - (iv) trifluoromethyl,
 - (3) —CH₂OR^a,
 - (4) —CH₂—O—CH₂CH₂Si(CH₃)₃,
- R^a is independently selected from:
- (1) hydrogen,
 - (2) C₁₋₆alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:

- (a) halo,
 (b) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
 (c) hydroxyl,
 (d) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 (e) —CN, and
 (f) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
- (i) halo,
 (ii) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
 (iii) —CN,
 (iv) nitro,
 (v) hydroxyl, and
 (vi) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
- (3) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
- (a) halo,
 (b) —CN,
 (c) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
 (d) nitro,
 (e) hydroxyl, and
 (f) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo, and
- (4) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo;
- R^b and R^c are independently selected from:
- (1) hydrogen,
 (2) C₁₋₆alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
- (a) halo,
 (b) —OR^a,
 (c) —CN,
 (d) —CO₂R^a,
 (e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
- (i) halo,
 (ii) —OR^a,
 (iii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo, and
 (iv) nitro,
- (3) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
- (a) halo,

- (b) —OR^a,
 (c) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
 (d) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 (e) —CN, and
 (f) —CO₂R^a,
- (4) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo;
 or R^b and R^c and the nitrogen to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:
- (a) halo,
 (b) —OR^a, and
 (c) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo, and
 (d) phenyl;
- R^d is independently selected from:
- (1) C₁₋₆alkyl, which is unsubstituted or substituted with 1-4 substituents each independently selected from:
- (a) halo,
 (b) —OR^a,
 (c) —CO₂R^a,
 (d) —CN, and
 (e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
- (i) halo,
 (ii) —OR^a,
 (iii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo, and
 (iv) nitro,
- (2) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
- (a) halo,
 (a) —OR^a,
 (b) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo,
 (c) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo
 (d) —CN, and
 (e) —CO₂R^a, and
- (3) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo;
- R^e and R^f are independently selected from:
- (1) hydrogen,
 (2) —C₁₋₄alkyl, which is unsubstituted or substituted with 1-6 halo,
 (3) —OR^a,
 (4) —CN,
 (5) halo,
 (6) phenyl, and
 (7) benzyl;
- and R^e and R^f and the carbon atom or atoms to which they are attached may join to form a 3-, 4-, 5-, or 6-membered

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ring optionally containing a heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

- (a) halo,
- (b) $-\text{OR}^a$,
- (c) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo, and
- (d) phenyl;

R^g and R^h are independently selected from:

- (1) $-\text{C}_{1-4}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
- (2) $-\text{OR}^a$,
- (3) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
- (4) phenyl, and
- (5) benzyl;

and R^g and R^h and the silicon atom to which they are attached may join to form a 3-, 4-, 5-, or 6-membered ring optionally containing a heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

- (a) halo,
- (b) $-\text{OR}^a$,
- (c) $-\text{C}_{1-4}$ alkyl, which is unsubstituted or substituted with 1-3 halo, and
- (d) phenyl;

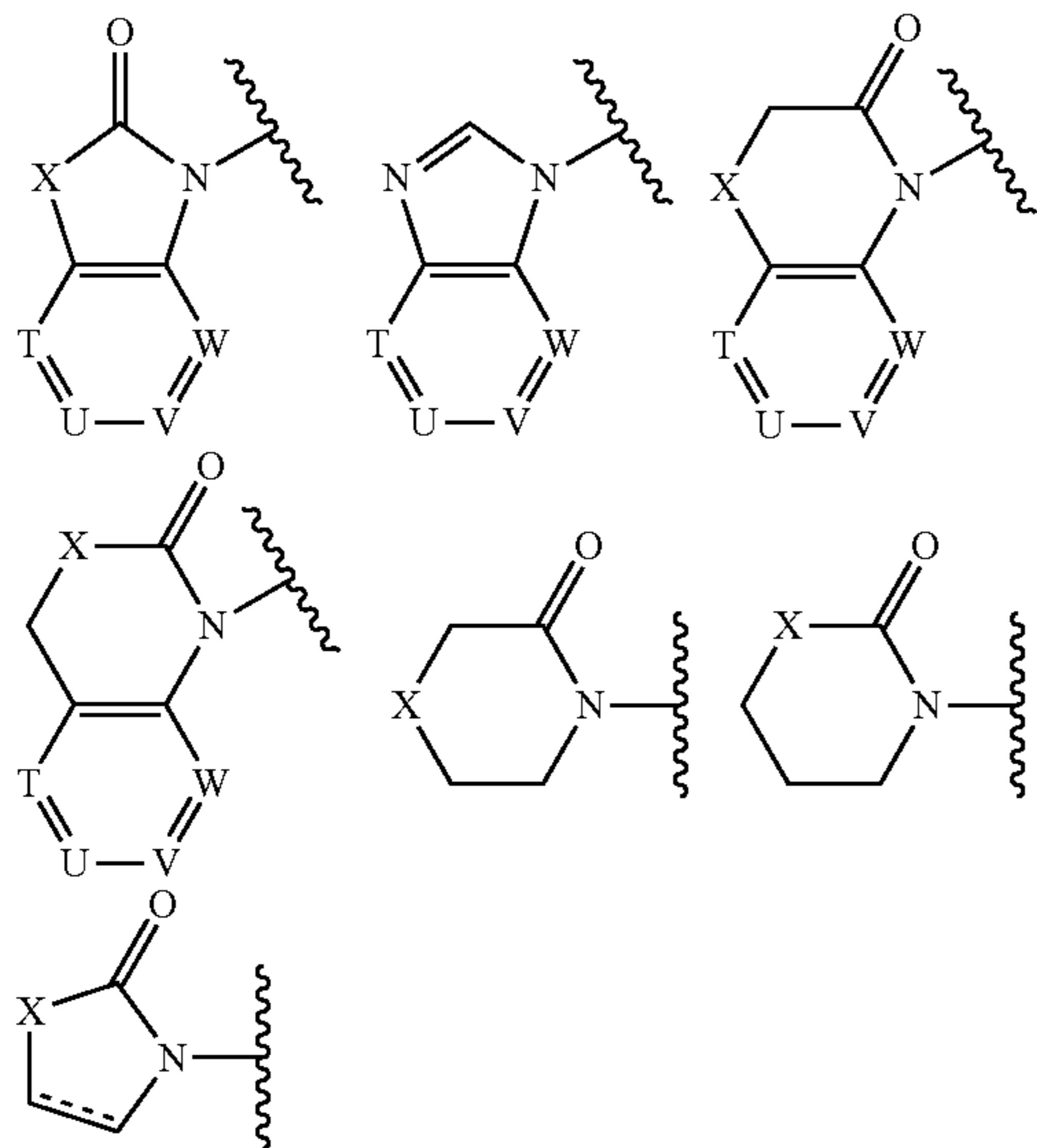
R^i and R^j are independently selected from:

- (1) hydrogen,
- (2) $-\text{C}_{1-4}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
- (3) $-\text{OR}^a$,
- (4) halo,
- (5) phenyl, and
- (6) benzyl;

q is 0, 1, or 2;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

In one embodiment of the present invention B is selected from the group consisting of:

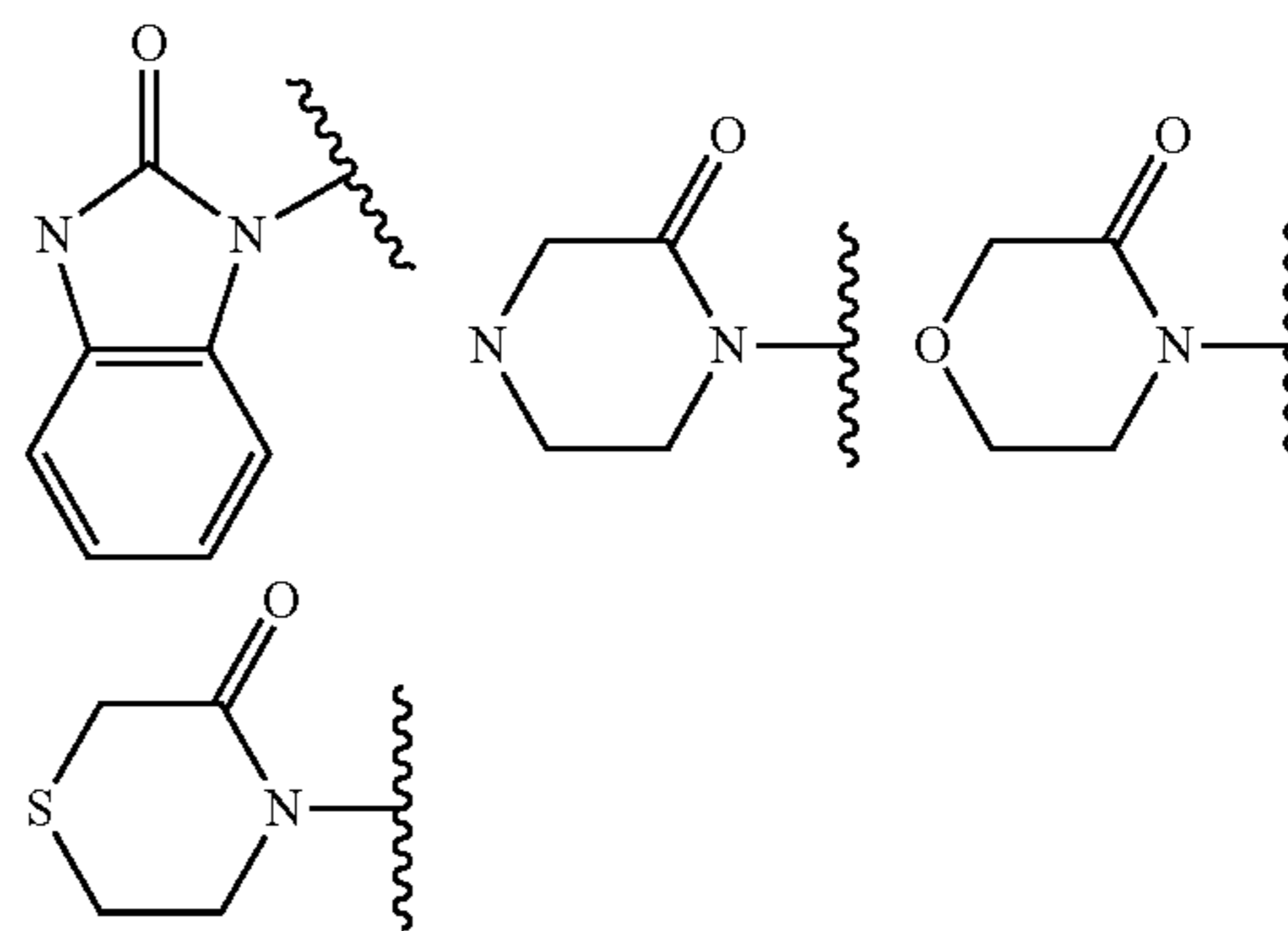


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which is unsubstituted or substituted with 1-7 substituents each independently selected from R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} , wherein T, U, V, W, X, R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} are defined herein,

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

In another embodiment of the present invention B is selected from the group consisting of:



which is unsubstituted or substituted with 1-7 substituents each independently selected from R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} , wherein R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} are defined herein, and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

In an embodiment of the present invention B is selected from 2-oxobenzimidazoliny, 2-oxopiperazinyl, 3-oxomorpholinyl and 3-oxothiomorpholinyl.

In an embodiment of the present invention R^1 , R^2 , and R^3 are each independently selected from:

- (1) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:

- (a) fluoro,
- (b) hydroxy,
- (c) $-\text{O}-\text{C}_{1-6}$ alkyl,
- (d) $-\text{C}_{3-6}$ cycloalkyl,
- (e) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, oxazolyl, thiazolyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from: $-\text{C}_{1-6}$ alkyl, $-\text{O}-\text{C}_{1-6}$ alkyl, halo, hydroxy, trifluoromethyl and $-\text{OCF}_3$,

- (f) $-\text{CO}_2\text{R}^{19}$,
- (g) $-\text{NR}^{20}\text{R}^{21}$,
- (h) $-\text{SO}_2\text{R}^{22}$,
- (i) $-\text{CONR}^{20a}\text{R}^{21a}$,
- (j) trifluoromethyl,
- (k) $-(\text{NR}^{20a})\text{CO}_2\text{R}^{19}$,
- (l) $-(\text{NR}^{19})(\text{CO})\text{NR}^{20a}\text{R}^{21a}$, and
- (m) $-\text{O}-\text{C}_{3-6}$ cycloalkyl,

- (2) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:

- (a) fluoro,
- (b) hydroxy,
- (c) $-\text{O}-\text{C}_{1-6}$ alkyl,
- (d) trifluoromethyl, and
- (e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: $-\text{C}_{1-6}$ alkyl, $-\text{O}-\text{C}_{1-6}$ alkyl, halo, hydroxy and trifluoromethyl,

(3) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, thienyl, pyridazinyl, pyrrolidinyl, azetidyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, azepanyl, benzimidazolyl, benzopyranyl, benzofuryl, benzothiazolyl, benzoxazolyl, chromanyl, furyl, imidazolyl, indolyl, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, isoindolyl, tetrahydroisoquinolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, pyrazolidinyl, pyrazolyl, pyrrolyl, quinazolyl, tetrahydrofuryl, thiazolyl, purinyl, naphthyridinyl, quinoxalyl, 1,3-dioxolanyl, oxadiazolyl, piperidinyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiopyranyl, and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (a) $-\text{CF}_3$,
 - (b) halo,
 - (c) hydroxy,
 - (d) $-\text{O}-\text{CF}_3$,
 - (e) $-\text{C}_{3-6}$ cycloalkyl,
 - (f) $-\text{CO}_2\text{R}^{19}$,
 - (g) $-(\text{CO})\text{R}^{19}$,
 - (h) $-\text{CONR}^{20}\text{R}^{21}$,
 - (i) oxo, and
 - (j) $\text{S}(\text{O})_q\text{R}^{22}$,
- (4) halo,
 - (5) oxo,
 - (6) hydroxy,
 - (7) $-\text{O}-\text{C}_{1-6}$ alkyl which is unsubstituted or substituted with 1-5 halo,
 - (8) $-\text{CN}$,
 - (9) $-\text{CO}_2\text{R}^{19}$,
 - (10) $-\text{NR}^{20}\text{R}^{21}$,
 - (11) $-\text{SO}_2\text{R}^{22}$,
 - (12) $-\text{CONR}^{20a}\text{R}^{21a}$,
 - (13) $-\text{SO}_2\text{NR}^{20a}\text{R}^{21a}$, and
 - (14) hydrogen.

In an embodiment of the present invention R^3 and R^4 and the carbon atom to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, dioxolanyl, dioxanyl, aziridinyl, azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, oxetanyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (a) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
 - (i) halo,
 - (ii) $-\text{OR}^a$,
 - (iii) $-\text{C}_{3-6}$ cycloalkyl,
 - (iv) $-\text{CO}_2\text{R}^a$,
 - (v) $-\text{NR}^b\text{R}^c$,
 - (vi) $-\text{S}(\text{O})_q\text{R}^d$,
 - (vii) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$, and
 - (viii) phenyl,

(b) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, wherein the phenyl or heterocycle is optionally fused to the ring, and which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (i) halo,
- (ii) $-\text{CF}_3$

- (iii) $-\text{OR}^a$,
- (iv) $-\text{CO}_2\text{R}^a$,
- (v) $-\text{O}(\text{C}=\text{O})\text{R}^a$,
- (vi) $-\text{CN}$,
- (vii) oxo, and
- (viii) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$,

- (c) halo,
- (d) $-\text{CO}_2\text{R}^a$,
- (e) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$,
- (1) $-\text{CN}$,
- (g) $-\text{C}(=\text{O})\text{R}^a$, and
- (h) oxo.

In an embodiment of the present invention X is selected from:

- (1) $-\text{O}-$,
- (2) $-\text{S}(\text{O})_q-$,
- (3) $-\text{N}(\text{R}^8)-$,
- (4) $-(\text{C}=\text{O})-$,
- (5) $-\text{C}(\text{R}^8)(\text{R}^a)-$,
- (6) $-\text{C}(\text{N}(\text{R}^b)-\text{SO}_2\text{R}^d)(\text{R}^a)-$,
- (7) $-\text{C}(\text{N}(\text{R}^b)(\text{C}=\text{O})\text{R}^a)(\text{R}^a)-$,
- (8) $-\text{C}(\text{N}(\text{R}^b)(\text{C}=\text{O})\text{OR}^a)(\text{R}^a)-$,
- (9) $-\text{CR}^{10}\text{R}^{11}-$,
- (10) $-\text{N}(\text{R}^{11})-$, and
- (11) $-\text{CR}^3\text{R}^4-$.

In an embodiment of the present invention A^1 and A^3 are independently selected from:

- (1) $-\text{O}-$,
- (2) $-\text{CR}^e\text{R}^f-$,
- (3) $-\text{N}(\text{R}^7)-$,
- (4) $-(\text{C}=\text{O})-$, and
- (5) a bond.

In an embodiment of the present invention A^1 and A^3 are a bond.

In an embodiment of the present invention A^2 and A^4 are independently selected from:

- (1) $-\text{O}-$,
- (2) $-\text{CR}^e\text{R}^f-$,
- (3) $-\text{N}(\text{R}^7)-$, and
- (4) $-(\text{C}=\text{O})-$.

In an embodiment of the present invention A^2 and A^4 are $-\text{CR}^e\text{R}^f-$,

In an embodiment of the present invention E^a , E^b , and E^c are each independently selected from:

- (1) $-\text{C}(\text{R}^5)=$, and
- (2) $-\text{N}=-$;

In an embodiment of the present invention E^a , E^b , and E^c are each independently selected from $-\text{C}(\text{R}^5)=$.

In an embodiment of the present invention G^1 is selected from:

- (1) a bond, and
- (2) $-\text{CR}^e\text{R}^f-$.

In an embodiment of the present invention G^1 is a bond.

In an embodiment of the present invention G^2 is selected from:

- (1) a bond,
- (2) $-\text{CR}^e\text{R}^f-$,
- (3) $-\text{C}(\text{R}^i)=\text{C}(\text{R}^i)-$, and
- (4) $-\text{C}\equiv\text{C}-$.

In an embodiment of the present invention G^2 is a bond.

In an embodiment of the present invention G^3 is selected from:

- (1) a bond,
- (2) $-\text{CR}^e\text{R}^f-$,
- (2) $-\text{C}(\text{R}^i)=\text{C}(\text{R}^i)-$,
- (4) $-\text{C}=\text{C}-$, and
- (5) $-(\text{C}=\text{O})-$.

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In an embodiment of the present invention G^4 is selected from:

- (1) $—CR^eR^f—$,
- (2) $—N(R^7)—$,
- (3) $—O—$,
- (4) $—S(O)_q—$,
- (5) $—C(R^i)=C(R^i)—$, and
- (6) $—C≡C—$.

In an embodiment of the present invention R^5 is selected from:

- (1) hydrogen,
- (2) $—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 - (a) halo,
 - (b) $—OC_{1-6}$ alkyl, and
 - (c) phenyl,
- (4) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) $—C_{1-4}$ alkyl, which is unsubstituted or substituted with 1-5 fluoro,
 - (b) halo,
 - (c) $—CN$,
 - (d) hydroxy, and
 - (e) $—O—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 fluoro,
- (5) halo,
- (6) hydroxy,
- (7) $—OC_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
- (8) $—CN$, and
- (9) $—CO_2R^{19}$.

In an embodiment of the present invention R^5 is selected from:

- (1) hydrogen,
- (2) $—CF_3$, and
- (3) halo.

In an embodiment of the present invention R^6 is selected from:

- (1) hydrogen
- (2) $—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 - (a) halo,
 - (b) $—O—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 fluoro,
 - (c) $—C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 fluoro, and
 - (d) phenyl or heterocycle, wherein heterocycle is selected from: benzimidazolyl, furanyl, imidazolyl, indolyl, morpholinyl, oxazolyl, oxadiazolyl, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, tetrahydrofuranyl, tetrahydrofuryl, tetrazolyl, thiazolyl, thienyl, isoxazolyl, tetrahydropyranyl, and triazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from: $—C_{1-6}$ alkyl, $—O—C_{1-6}$ alkyl, halo, hydroxy, trifluoromethyl, $—CN$, and $—OCF_3$,
- (3) phenyl or heterocycle, wherein heterocycle is selected from: benzimidazolyl, furanyl, imidazolyl, indolyl, morpholinyl, oxazolyl, oxadiazolyl, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl,

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pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, tetrahydrofuranyl, tetrahydrofuryl, tetrazolyl, thiazolyl, thienyl, isoxazolyl, tetrahydropyranyl, and triazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

- (a) halo,
- (b) $—OR^a$,
- (c) $—CO_2R^a$,
- (d) $—C(=O)NR^bR^c$,
- (e) $—CN$,
- (f) $—N(R^b)C(=O)R^a$,
- (g) $—N(R^b)SO_2R^d$, and
- (h) $—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
- (4) $—C_{1-6}$ cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) halo,
 - (b) $—CN$, and
 - (c) $—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo.

In an embodiment of the present invention R^6 is phenyl or pyridyl.

In an embodiment of the present invention R^7 is selected from:

- (1) hydrogen,
- (2) $—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) halo,
 - (b) $—C_{3-6}$ cycloalkyl,
 - (c) $—CF_3$, and
 - (d) $—O—R^a$,
- (3) $—C_{3-6}$ cycloalkyl.

In an embodiment of the present invention R^7 is hydrogen or methyl.

In an embodiment of the present invention R^8 is selected from:

- (1) hydrogen,
- (2) $—C(=O)R^a$,
- (3) $—CO_2R^a$,
- (4) $—S(=O)R^d$,
- (5) $—SO_2R^d$,
- (6) $—C(=O)NR^bR^c$,
- (7) $—C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
- (8) $—C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 - (a) halo,
 - (b) $—CN$,
 - (c) OR^a , and
 - (d) C_{1-6} alkyl, which is unsubstituted or substituted with 1-6 halo.

In an embodiment of the present invention R^8 is hydrogen, methyl or $—C(=O)R^a$.

In an embodiment of the present invention R^4 and R^8 and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

- (a) halo,
- (b) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a , CN , and $—C(=O)OR^a$,

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- (c) —OR^a, and
 (d) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo.

In an embodiment of the present invention R⁴ and R⁸ and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

- (a) halo, and
 (b) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo.

In an embodiment of the present invention R¹⁰ is selected from:

- (a) hydrogen, and
 (b) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro;

In an embodiment of the present invention R¹⁰ is hydrogen.

In an embodiment of the present invention R¹¹ is independently selected from the group consisting of:

phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl, azepinyl, azepanyl, azetidiny, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, chromanyl, cinnoliny, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, furanyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, morpholiny, naphthyridiny, oxadiazolyl, 2-oxoazepiny, 4-oxonaphthyridiny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxopyridyl, 2-oxoquinoliny, piperidyl, piperaziny, pyraziny, pyrazolidiny, pyrazolyl, pyridaziny, pyridiny, pyridyl, pyrimidiny, pyrimidyl, pyrrolidiny, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridiny, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, thiamorpholiny, thiamorpholiny sulfone, thiamorpholiny sulfone, thiazolyl, thiazoliny, thienofuryl, thienothienyl, thienyl, triazolyl, isoxazolyl, tetrahydrothienyl, tetrahydropyranyl, oxetanyl, tetrahydrothiapyranyl, and thietanyl, where R¹¹ is unsubstituted or substituted with 1-5 substituents each independently selected from R¹², R¹³, R¹⁴, R^{15a} and R^{15b}, wherein R¹², R¹³, R¹⁴, R^{15a} and R^{15b} are defined herein;

In an embodiment of the present invention R¹¹ is independently selected from the group consisting of:

phenyl, pyridyl, and thienyl, where R¹¹ is unsubstituted or substituted with 1-5 substituents each independently selected from R¹², R¹³, R¹⁴, R^{15a} and R^{15b}, wherein R¹², R¹³, R¹⁴, R^{15a} and R^{15b} are defined herein.

In an embodiment of the present invention R¹¹ is phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from R¹², R¹³, R¹⁴, R^{15a} and R^{15b}, wherein R¹², R¹³, R¹⁴, R^{15a} and R^{15b} are defined herein.

In an embodiment of the present invention R^{PG} is selected from:

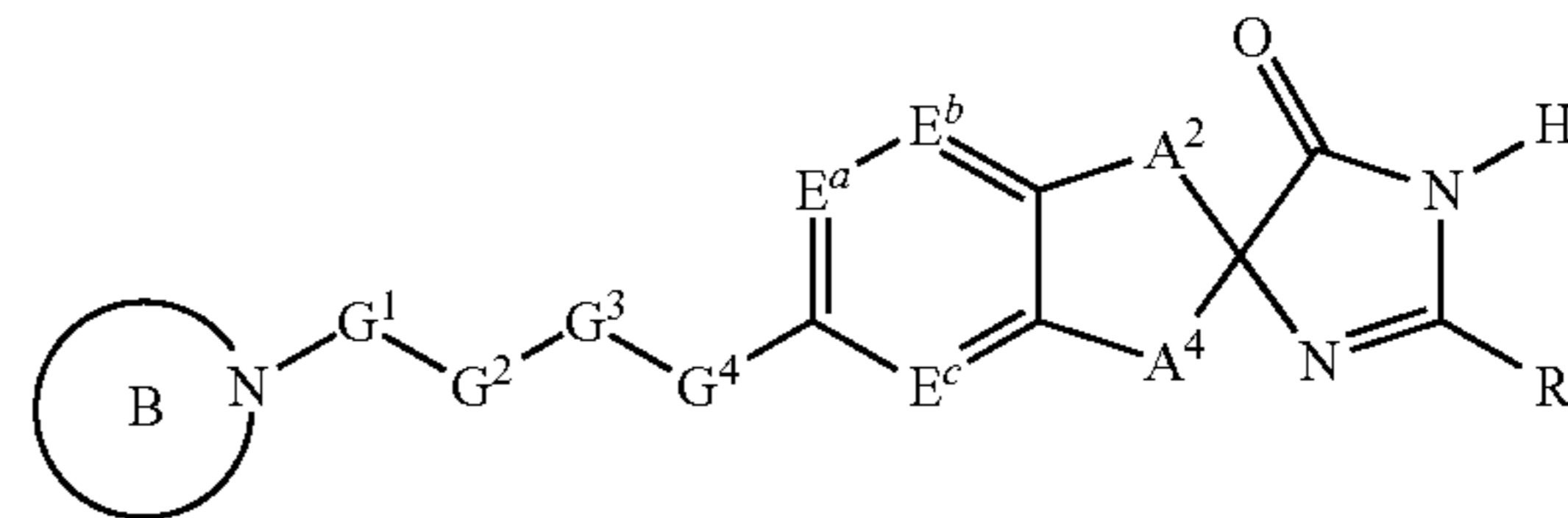
- (1) hydrogen,
 (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-3 halo,
 (3) —CH₂OR^a, and
 (4) —CH₂—O—CH₂CH₂Si(CH₃)₃;

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In an embodiment of the present invention R^{PG} is methyl or hydrogen,

Another embodiment of the invention includes compounds of formula IA:

IA

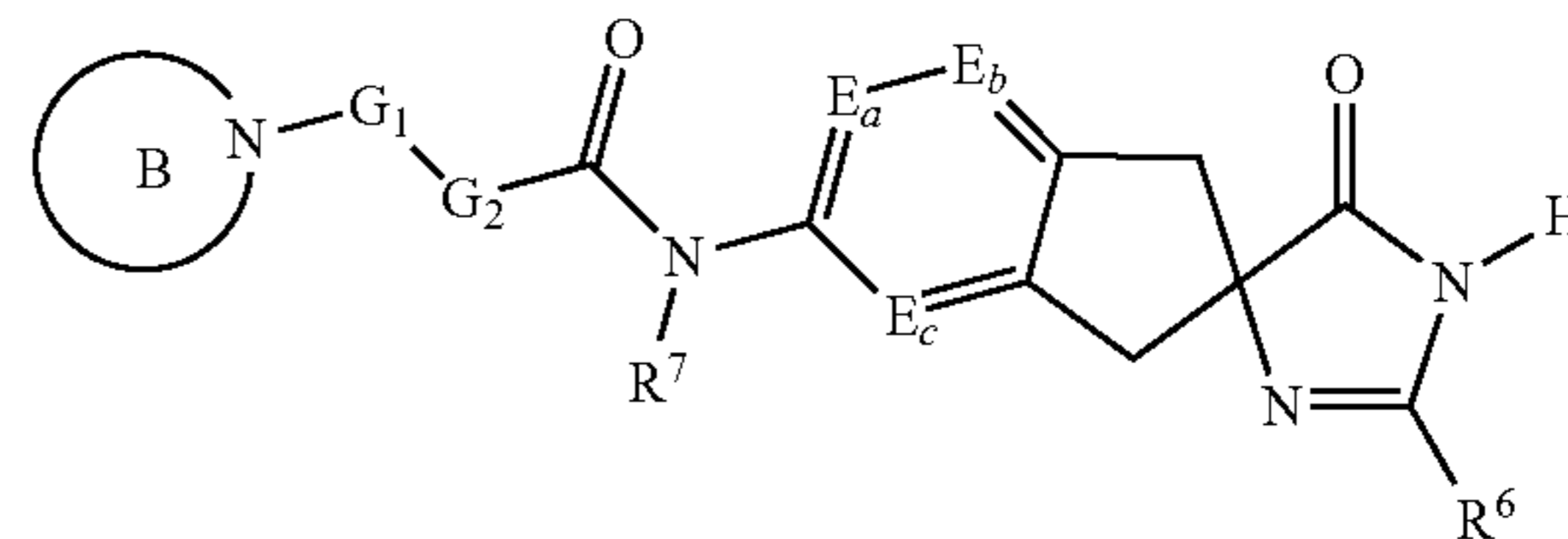


wherein A², A⁴, B, E^a, E^b, E^c, G¹, G², G³, G⁴, and R⁶ are defined herein;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

Another embodiment of the invention includes compounds of formula IB:

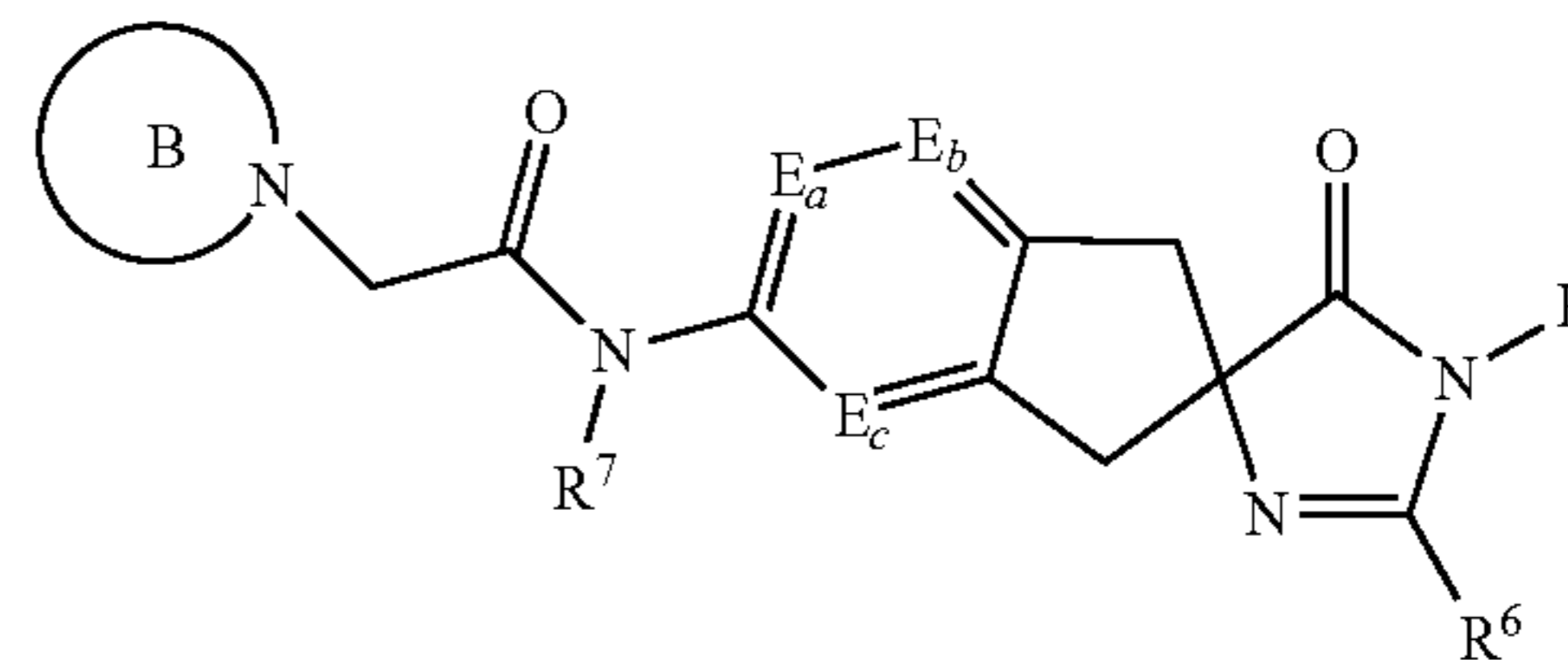
IB



wherein B, E^a, E^b, E^c, G¹, G², R⁶, and R⁷ are defined herein; and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

Another embodiment of the invention includes compounds of formula IC:

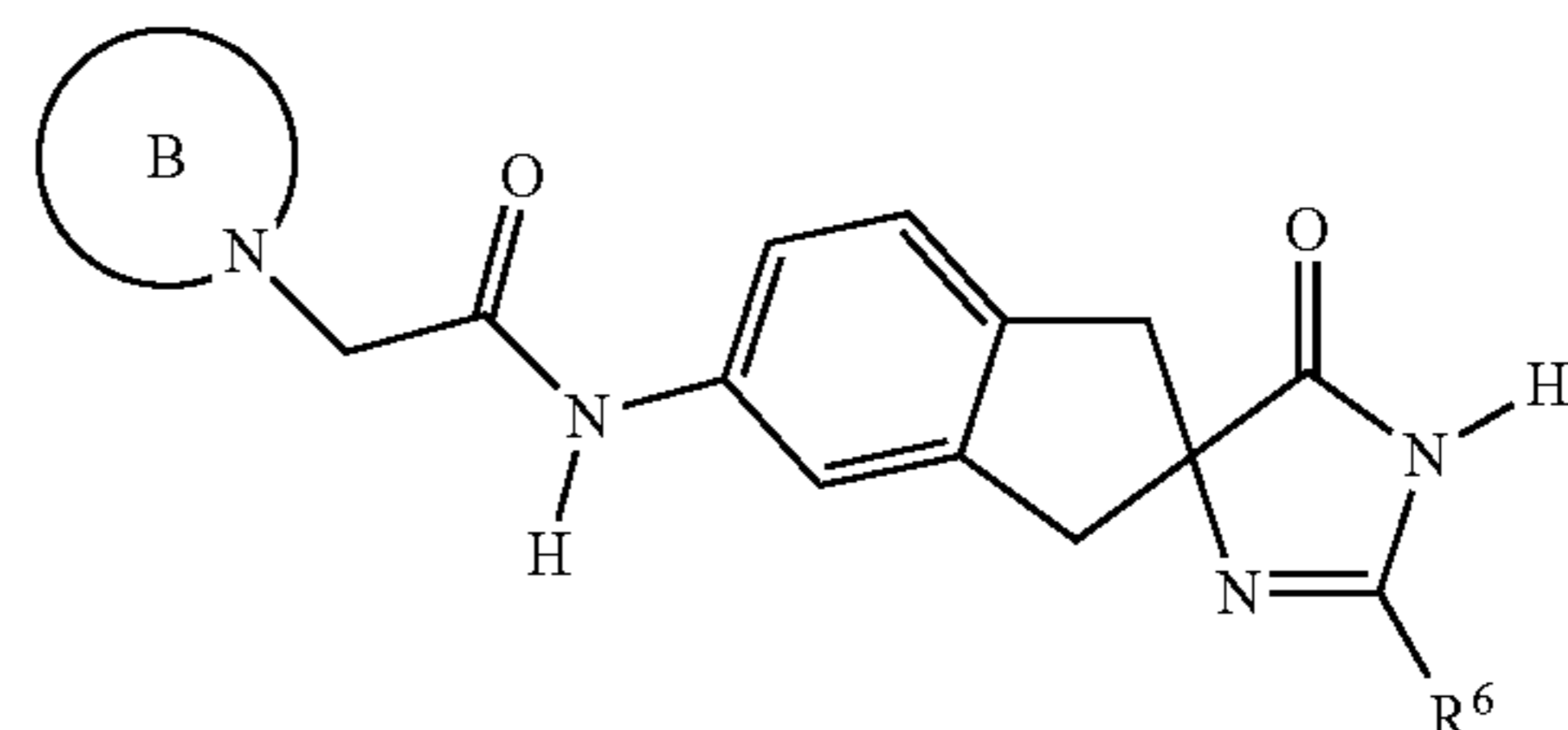
IC



wherein B, E^a, E^b, R⁶, and R⁷ are defined herein; and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

Another embodiment of the invention includes compounds of formula ID:

ID



wherein B and R⁶ are defined herein; and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

The present invention is further directed to the exemplary compounds 1-13, or a pharmaceutically acceptable salt thereof.

The invention is also directed to medicaments or pharmaceutical compositions for treating diseases or disorders in which CGRP is involved, such as migraine, which comprise a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention is also directed to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for treating diseases or disorders in which CGRP is involved, such as migraine.

The invention is further directed to the use of a compound of the invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament or a composition for treating diseases or disorders in which CGRP is involved, such as migraine, by combining a compound of formula (I) with one or more pharmaceutically acceptable carriers.

It is to be understood that where one or more of the above recited structures or substructures recite multiple substituents having the same designation each such variable may be the same or different from each similarly designated variable. For example, R⁹ is recited multiple times in certain configurations of formula I, and each instance of R⁹ in formula I may independently be any of the substructures defined under R⁹. The invention is not limited to structures and substructures wherein each R⁹ must be the same for a given structural configuration. The same is true with respect to any variable appearing multiple times in a structure or substructure.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The present invention includes compounds of formula I wherein one or more hydrogen atoms are replaced by deuterium. Tautomers of compounds defined in Formula I are also included within the scope of the present invention. For example, compounds including carbonyl —CH₂C(O)— groups (keto forms) may undergo tautomerism to form hydroxyl —CH=C(OH)— groups (enol forms). Both keto and enol forms are included within the scope of the present invention.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo.

As used herein, “alkyl” is intended to mean linear or branched structures having no carbon-to-carbon double or triple bonds. Thus C₁₋₆alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C₆alkyl specifically includes, but is not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl and hexyl. “Cycloalkyl” is an alkyl, part or all of which which forms a ring of three or more atoms. C₀ or C₀alkyl is defined to identify the presence of a direct covalent bond.

As used herein, “aryl” is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, or biphenyl.

The term “heterocycle” or “heterocyclic”, as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 8- to 11-membered bicyclic heterocyclic ring system which is either saturated or unsaturated, and which consists of carbon atoms and from one to six heteroatoms selected from the group consisting of N, O, S, P and Si, and wherein the nitrogen, sulfur and phosphorus heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicycle group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

When a heterocyclic group as defined herein is substituted, the substituent may be bonded to a ring carbon atom of the heterocyclic group, or on a ring heteroatom (i.e., a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Similarly, when a heterocyclic group is defined as a substituent herein, the point of attachment may be at a ring carbon atom of the heterocyclic group, or on a ring heteroatom (i.e., a nitrogen, oxygen or sulfur), which has a valence which permits attachment.

The term “alkoxy,” as in C₁-C₆ alkoxy, includes alkoxy groups of from 1 to 6 carbon atoms of a straight, branched and cyclic configuration. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, “pharmaceutically acceptable salts” refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceuti-

cally acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In one aspect of the invention the salts are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The subject compounds are useful in a method of antagonism of CGRP receptors in a patient such as a mammal in need of such antagonism comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as antagonists of CGRP receptors. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

Another embodiment of the present invention is directed to a method for the treatment, control, amelioration, or reduction of risk of a disease or disorder in which the CGRP receptor is involved in a patient that comprises administering to the patient a therapeutically effective amount of a compound that is an antagonist of CGRP receptors.

The present invention is further directed to a method for the manufacture of a medicament for antagonism of CORP receptors activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, for example a human being, male or female, in whom antagonism of CGRP receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product

which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the terms "administration of" or "administering a" compound shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The ability of the compounds of the present invention to act as CORP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: headache; migraine; cluster headache; chronic tension type headache; pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; diabetes; non-insulin dependent diabetes mellitus; vascular disorders; inflammation; arthritis; bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases; neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and other conditions that may be treated or prevented by antagonism of CORP receptors. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I or II is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also include therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the

other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

For example, the present compounds may be used in conjunction with an anti-migraine agent, such as ergotamine and dihydroergotamine, or other serotonin agonists, especially a 5-HT^{1B/1D} agonist, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, and rizatriptan, a 5-HT_{1D} agonist such as PNU-142633 and a 5-HT_{1F} agonist such as LY334370; a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, for example rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib; a non-steroidal anti-inflammatory agent or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as ibuprofen, ketoprofen, fenoprofen, naproxen, indomethacin, sulindac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac, etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenbutazone, diflunisal, salsalate, olsalazine or sulfasalazine and the like; or glucocorticoids. Similarly, the instant compounds may be administered with an analgesic such as aspirin, acetaminophen, phenacetin, fentanyl, sufentanil, methadone, acetyl methadol, buprenorphine or morphine.

Additionally, the present compounds may be used in conjunction with an interleukin inhibitor, such as an interleukin-1 inhibitor; an NK-1 receptor antagonist, for example aprepitant; an NMDA antagonist; an NR2B antagonist; a bradykinin-1 receptor antagonist; an adenosine A1 receptor agonist; a sodium channel blocker, for example lamotrigine; an opiate agonist such as levomethadyl acetate or methadyl acetate; a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase; an alpha receptor antagonist, for example indoramin; an alpha receptor agonist; a vanilloid receptor antagonist; a renin inhibitor; a granzyme B inhibitor; a substance P antagonist; an endothelin antagonist; a norepinephrin precursor; anti-anxiety agents such as diazepam, alprazolam, chlordiazepoxide and chlorazepate; serotonin 5HT₂ receptor antagonists; opioid agonists such as codeine, hydrocodone, tramadol, dextropropoxyphene and febtanyl; an mGluR5 agonist, antagonist or potentiator; a GABA A receptor modulator, for example acamprosate calcium; nicotinic antagonists or agonists including nicotine; muscarinic agonists or antagonists; a selective serotonin reuptake inhibitor, for example fluoxetine, paroxetine, sertraline, duloxetine, escitalopram, or citalopram; an antidepressant, for example amitriptyline, nortriptyline, clomipramine, imipramine, venlafaxine, doxepin, protriptyline, desipramine, trimipramine, or imipramine; a leukotriene antagonist, for example montelukast or zafirlukast; an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide.

Also, the present compounds may be used in conjunction with gap junction inhibitors; neuronal calcium channel blockers such as civamide; AMPA/KA antagonists such as LY293558; sigma receptor agonists; and vitamin B2.

Also, the present compounds may be used in conjunction with ergot alkaloids other than ergotamine and dihydroergotamine, for example ergonovine, ergonovine, methyle-
ergonovine, metergoline, ergoloid mesylates, dihydroergocor-
nine, dihydroergocristine, dihydroergocryptine, dihydro- α -
ergocryptine, dihydro- β -ergocryptine, ergotoxine,

ergocornine, ergocristine, ergocryptine, α -ergocryptine, β -ergocryptine, ergosine, ergostane, bromocriptine, or methysergide.

Additionally, the present compounds may be used in con-
5 junction with a beta-adrenergic antagonist such as timolol, propanolol, atenolol, metoprolol or nadolol, and the like; a MAO inhibitor, for example phenelzine; a calcium channel blocker, for example flunarizine, diltiazem, amlodipine, felodipine, nisolipine, isradipine, nimodipine, lomerizine, verapamil, nifedipine, or prochlorperazine; neuroleptics such as olanzapine, droperidol, prochlorperazine, chlorpromazine and quetiapine; an anticonvulsant such as topiramate, zonisamide, tonabersat, carabersat, levetiracetam, lamotrigine, tiagabine, gabapentin, pregabalin or divalproex sodium; an
10 anti-hypertensive such as an angiotensin H antagonist, for example losartan, irbesartan, valsartan, eprosartan, telmisartan, olmesartan, medoxomil, candesartan and candesartan cilexetil, an angiotensin I antagonist, an angiotensin converting enzyme inhibitor such as lisinopril, enalapril, captopril,
15 benazepril, quinapril, perindopril, ramipril andtrandolapril; or botulinum toxin type A or B.

The present compounds may be used in conjunction with a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as
25 oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antitussive such as caramiphen, carbetapentane, or dextromethorphan; a diuretic; a prokinetic agent such as metoclopramide or domperidone; a sedating or non-sedating antihistamine such as
30 acrivastine, azatadine, bromodiphenhydramine, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, loratadine, phenindamine, pheniramine, phenyltoloxamine, promethazine, pyrillamine, terfenadine, triprolidine, phenylephrine, phenylpropanolamine, or pseudoephedrine. The present compounds also may be
35 used in conjunction with anti-emetics.

In a particularly preferred embodiment the present compounds are used in conjunction with an anti-migraine agent, such as: ergotamine or dihydroergotamine; a 5-HT₁ agonist, especially a 5-HT_{1B/1D} agonist, in particular, sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, avitriptan and rizatriptan, and other serotonin
40 agonists; and a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, in particular, rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used there-
45 fore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

50 The weight ratio of the compound of the compound of the present invention to the other active ingredient(s) may be varied and will depend upon the effective dose of each ingre-

dient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, or from about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s), and via the same or different routes of administration.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, solutions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer

period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Oral tablets may also be formulated for immediate release, such as fast melt tablets or wafers, rapid dissolve tablets or fast dissolve films.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or

sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions and the like, containing the compounds of the present invention are employed. Similarly, transdermal patches may also be used for topical administration.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require antagonism of CGRP receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, or may be administered once or twice per day.

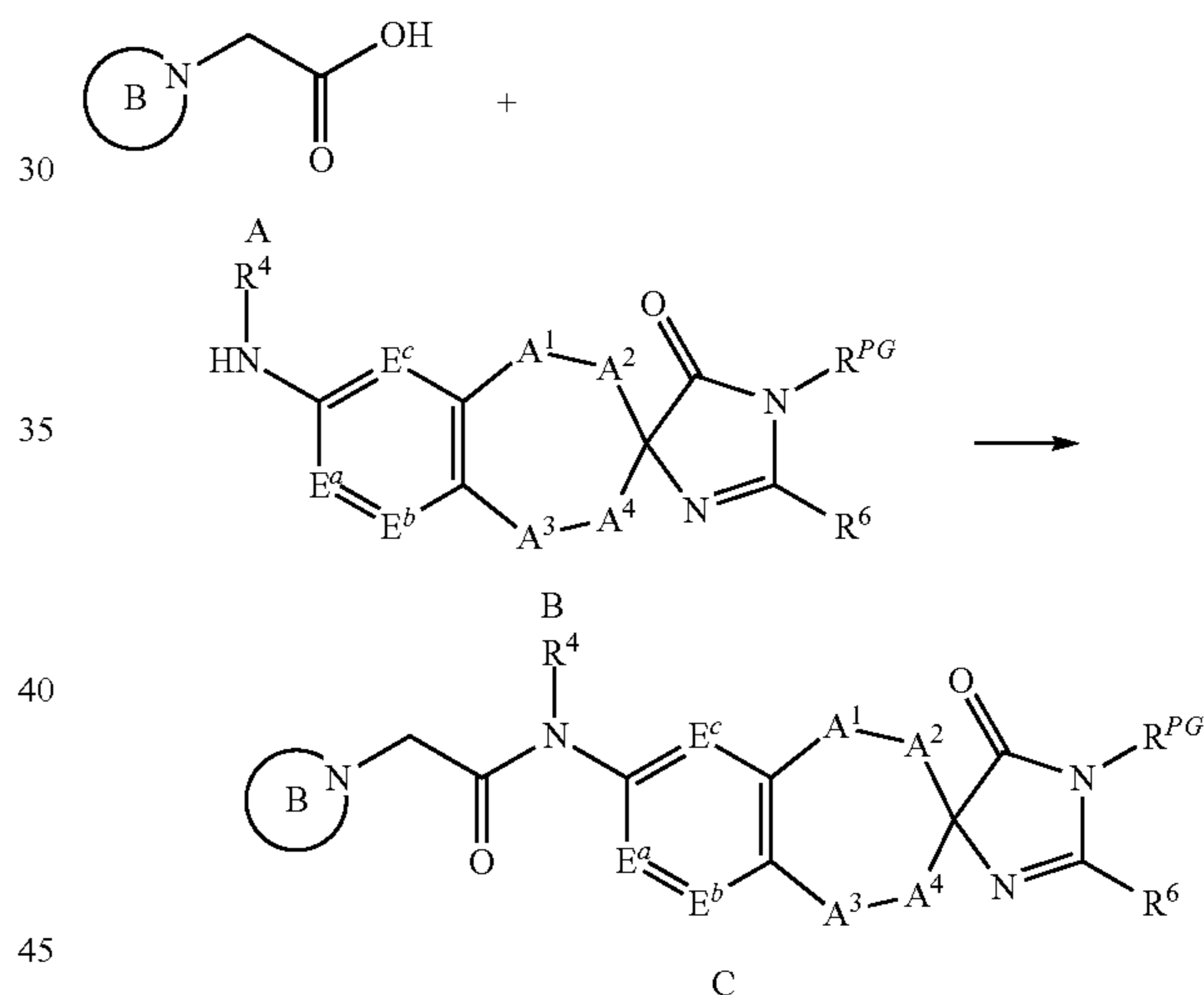
When treating, preventing, controlling, ameliorating, or reducing the risk of headache, migraine, cluster headache, or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, or from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes.

SCHEME 1

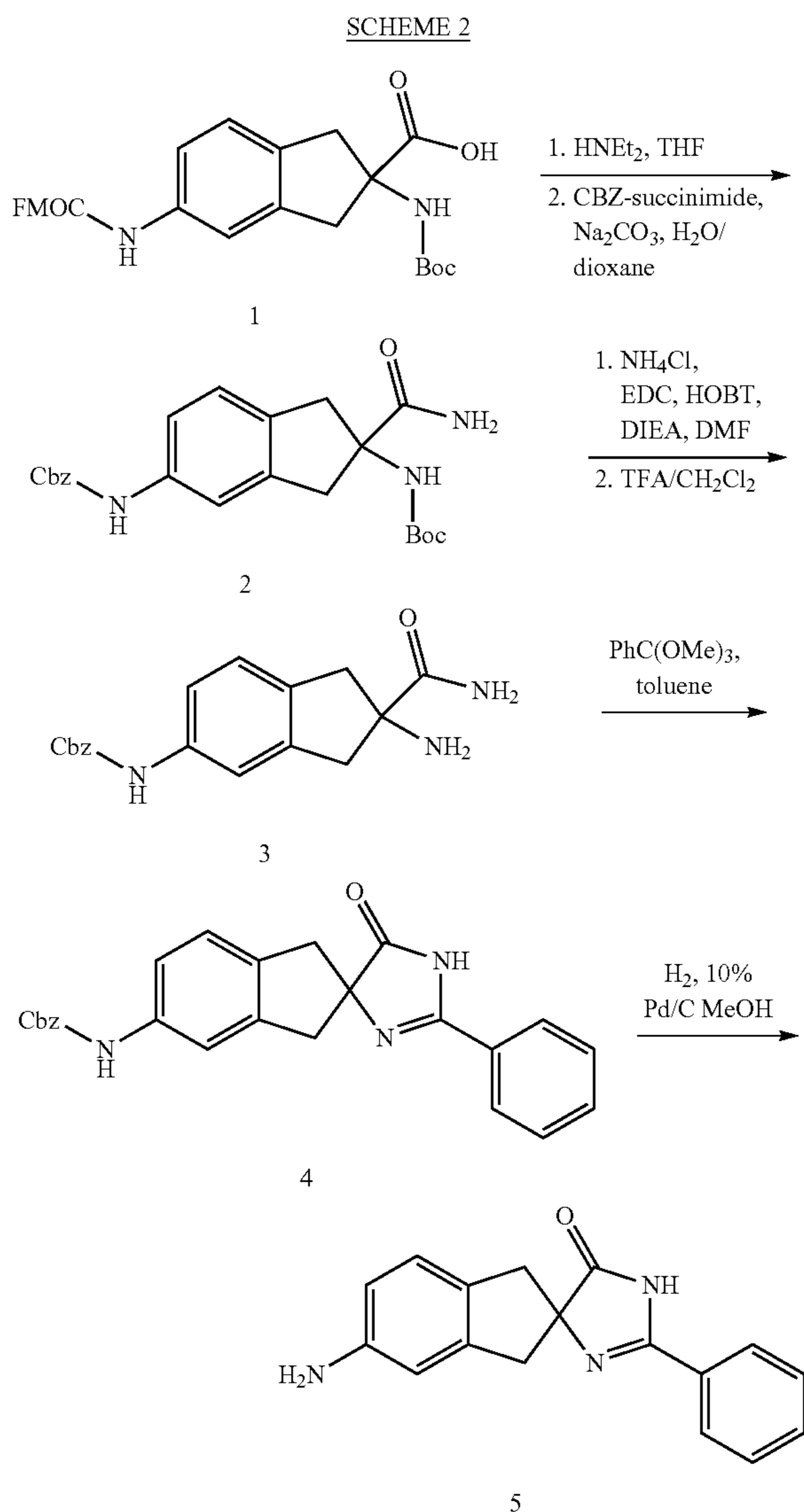


Scheme 1 illustrates a general strategy for the synthesis of the compounds of the present invention via coupling of carboxylic acid A with amine B to give amide C. Standard coupling conditions, such as EDC and HOBt with DIEA as base and DMF as solvent, may be successfully employed in this reaction. Other standard coupling conditions may be employed in the synthesis of such amides, including use of an alternative coupling reagent such as BOP, HATU or PyCLU, or activation of the carboxylic acid as an acid anhydride or acid chloride. In some cases, various protecting group strategies familiar to one skilled in the art of organic synthesis may be employed to allow preparation of a particular compound of the present invention.

Most of the acids A used to make the compounds of the present invention are readily available. They may be obtained from commercial sources or synthesized by methodology familiar to those skilled in the art and as described in the chemical literature. Many of the acids A of interest are also described in Wood et al WO 2008/020902 and Bell et al, U.S. Pat. No. 7,202,251.

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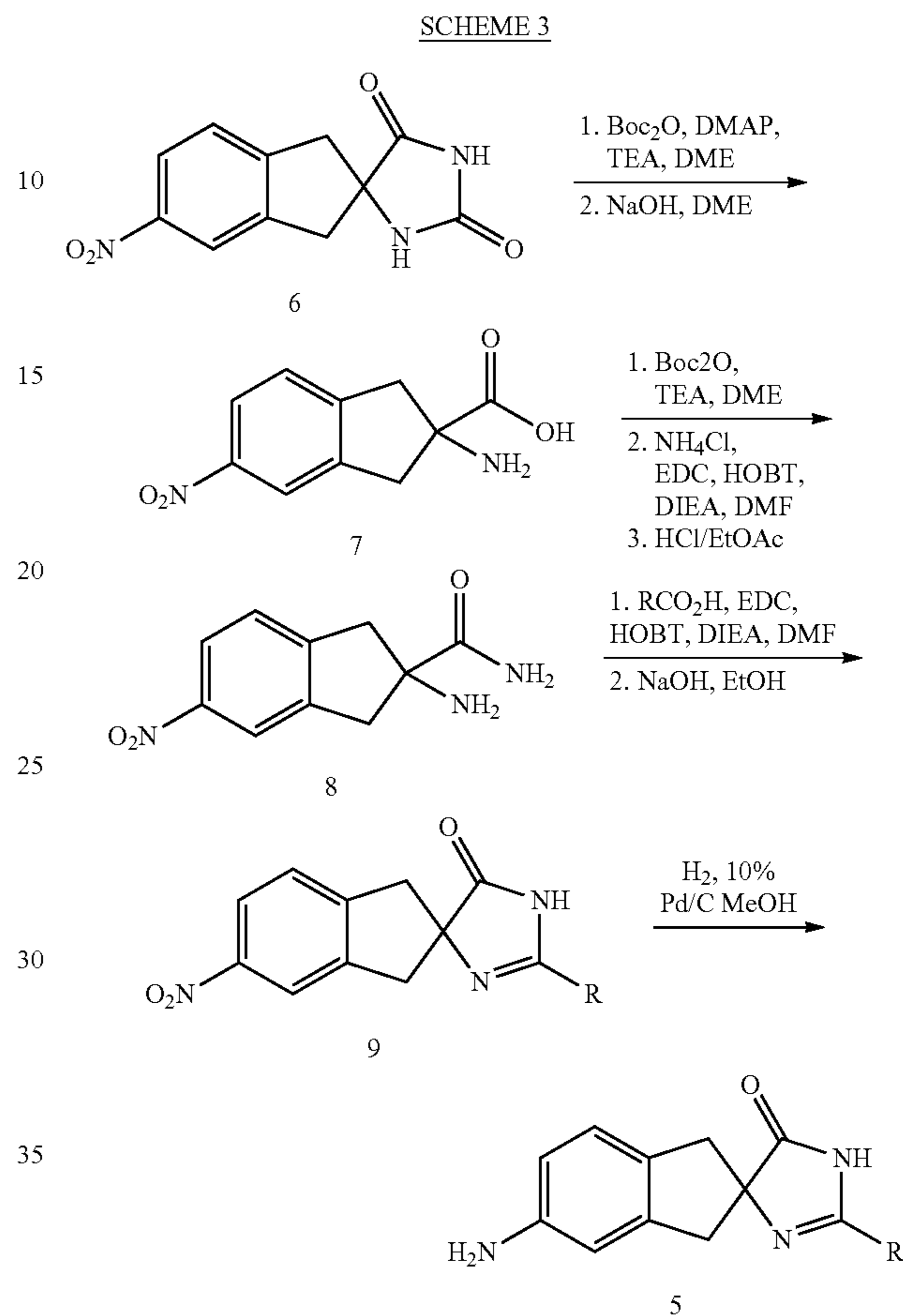
The synthesis of amine intermediates may be conducted as described in Schemes 2-3. Amine intermediates bearing a variety of substituents may be prepared by employing appropriately substituted starting materials or by derivatization of any intermediates and/or final products as desired by methods known in the art.



The synthesis of a representative spiroimidazolone aniline (5) is illustrated in Scheme 2. The commercially available indane (1) can be alternately protected as the CBZ carbamate (2). Conversion of the carboxylic acid to the primary amide followed by Boc deprotection can produce the α -aminoamide 3, which cyclizes to the imidazolone 4 after treatment with (trimethoxymethyl)benzene and heating in toluene. The reaction of aldehyde 3 with orthoesters other than (trimethoxymethyl)benzene may be used to provide a variety of substituted imidazolones 4. The intermediate 4 may be deprotected to provide aniline 5 using a variety of well known methodologies, such as catalytic hydrogenation. Those skilled in the art of organic synthesis will recognize that straightforward modifications of this methodology may be used to access other spiroimidazolone intermediates. Additionally, use of an

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alternative starting material to the indane 1 may be used to provide different products, such as tetralin-based spiroimidazolones.



In Scheme 3, an alternate route to the synthesis of a spiroimidazolone intermediate is shown. Treatment of hydantoin 6 (Bell et al. (2006) *Bioorg. Med. Chem. Lett.* 16, 6165) with Boc anhydride followed by hydrolysis with NaOH leads to indanyl amino acid 7. Protection of the primary amine, followed by conversion of the carboxylic acid to the primary amide and subsequent deprotection may produce intermediate 8. A variety of ways may be used to form the spiroimidazolone ring (9), one of which is via amide coupling to a carboxylic acid, followed by base catalyzed cyclization. Another method may be reaction with an acid chloride, followed by base catalyzed cyclization. The nitro intermediate 9 may be reduced to provide aniline 5 using a variety of well known methodologies, such as catalytic hydrogenation. Alternate reduction conditions using tin or iron may also be used for the conversion of 9 to 5.

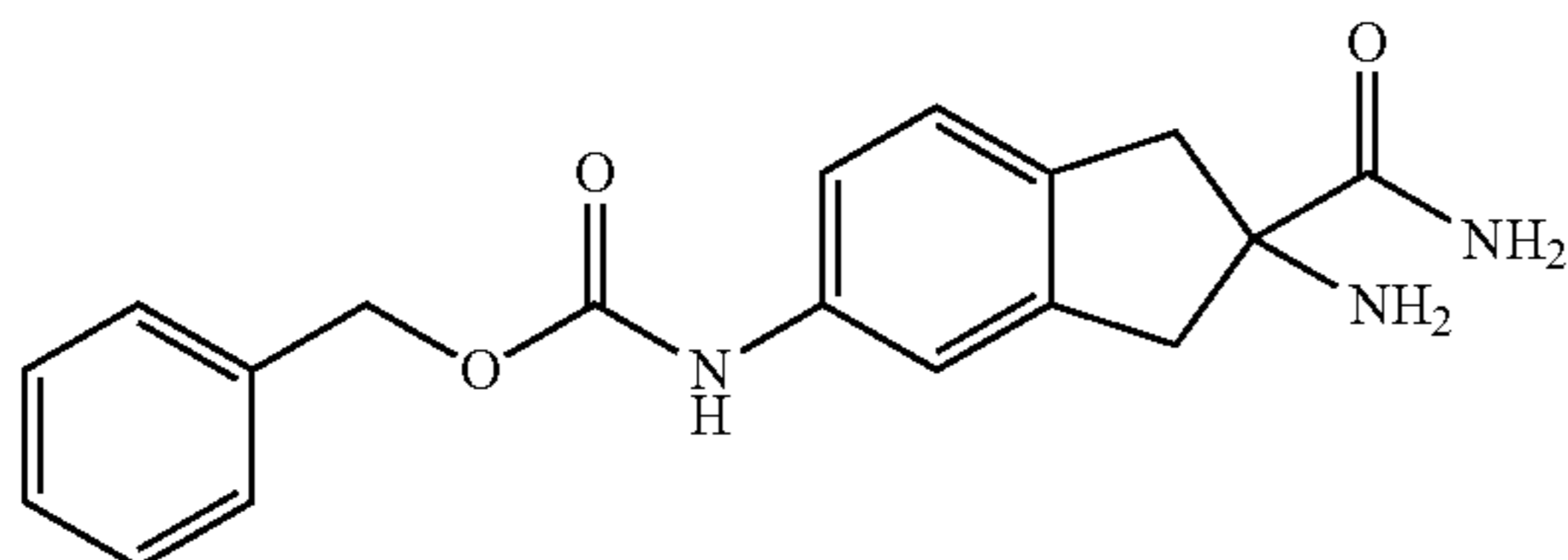
In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully under-

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stood. These examples are illustrative only and should not be construed as limiting the invention in any way.

Intermediate 1



(±)-Benzyl[2-amino-2-(aminocarbonyl)-2,3-dihydro-1H-inden-5-yl]carbamate

Step A. (±)-5-Amino-2-[(tert-butoxycarbonyl)amino]indane-2-carboxylic acid

Diethylamine (2.01 mL, 19.4 mmol) was added to a solution of (±)-2-[(tert-butoxycarbonyl)amino]-5-[(9H-fluoren-9-ylmethoxy)carbonyl]amino}indane-2-carboxylic acid (1.00 g, 1.94 mmol) in THF (5 mL) at ambient temperature and the mixture was stirred for 3 h. The reaction mixture was poured onto 1N NaOH (30 mL) and extracted with EtOAc (3×30 mL). The aqueous layer was acidified with concentrated HCl and extracted with CH₂Cl₂ (3×30 mL) and the combined CH₂Cl₂ layers were dried over Na₂SO₄, filtered, concentrated and dried under high vacuum to give the title compound. MS: m/z=293 (M+1).

Step B. (±)-5-[(benzyloxy)carbonyl]amino}-2-[(tert-butoxycarbonyl)amino]indane-2-carboxylic acid

To a solution of (±)-5-amino-2-[(tert-butoxycarbonyl)amino]indane-2-carboxylic acid from Step A (568 mg, 1.94 mmol) in dioxane (16 mL) and water (4 mL) was added sodium carbonate (412 mg, 3.89 mmol) and 1-[(benzyloxy)carbonyl]oxy}pyrrolidine-2,5-dione (533 mg, 2.14 mmol). The reaction was stirred at ambient temperature for 16 h, then poured onto saturated NH₄Cl (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and dried under high vacuum to give the title compound. MS: m/z=449 (M+Na).

Step C. (±)-Benzyl tert-butyl[2-(aminocarbonyl)-2,3-dihydro-1H-indene-2,5-diyl]biscarbamate

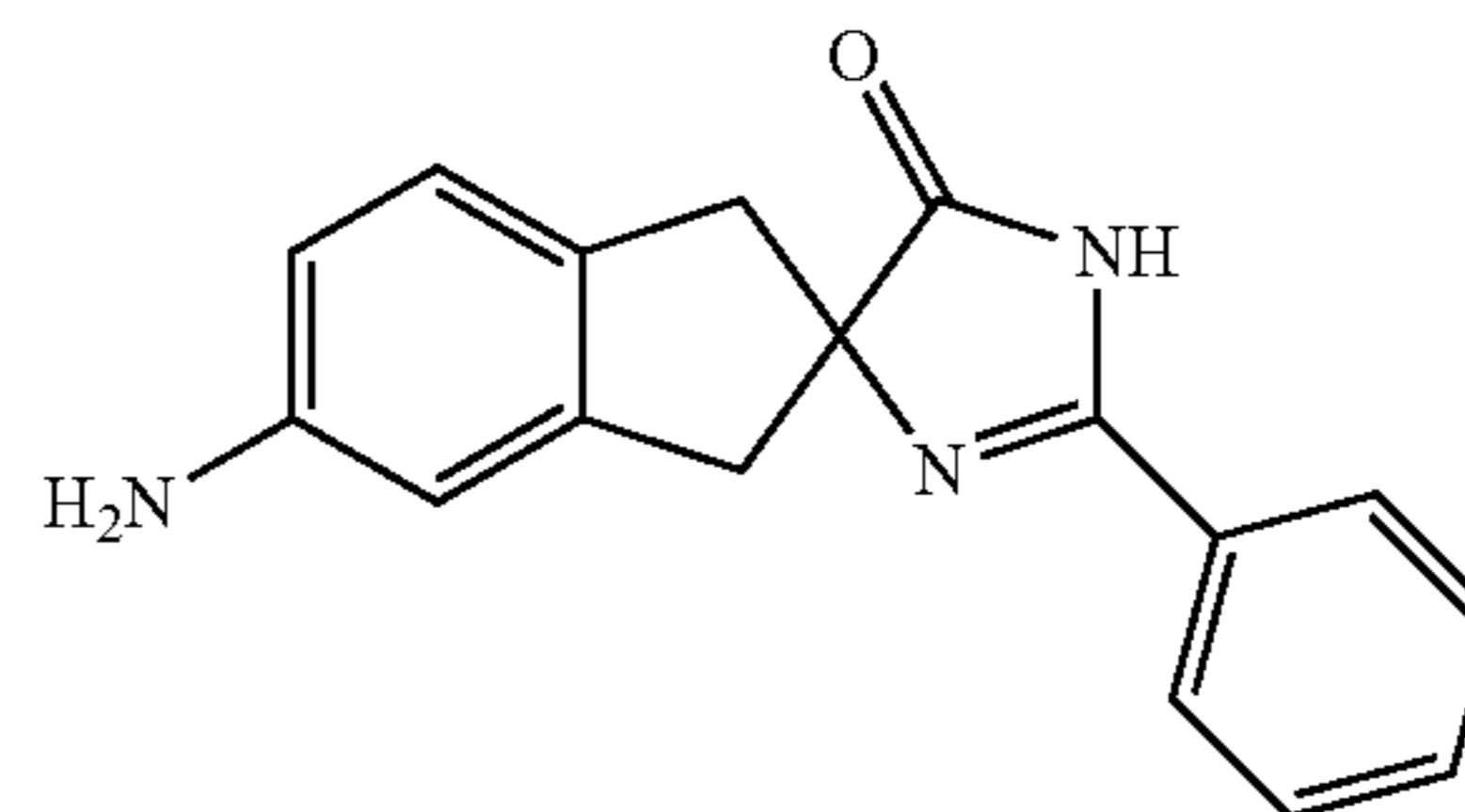
A solution of (±)-5-[(benzyloxy)carbonyl]amino}-2-tert-butoxycarbonyl]amino]indane-2-carboxylic acid from Step B (829 mg, 1.94 mmol), ammonium chloride (208 mg, 3.89 mmol), pyBOP (1.52 g, 2.92 mmol), and DIEA (1.35 mL, 7.78 mmol) in DMF (3 mL) was stirred at ambient temperature for 16 h. The reaction mixture was poured onto saturated NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3×20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of CH₂Cl₂:MeOH:NH₄OH—100:0:0 to 90:9:1, to give the title compound, MS: m/z=426 (M+1).

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Step D. (±)-Benzyl[2-amino-2-(aminocarbonyl)-2,3-dihydro-1H-inden-5-yl]carbamate

A solution of (±)-benzyl tert-butyl[2-(aminocarbonyl)-2,3-dihydro-1H-indene-2,5-diyl]biscarbamate from Step C (670 mg, 1.58 mmol) in CH₂Cl₂ (5 mL) and TFA (1 mL) was stirred for 16 h. The reaction mixture was poured onto saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3×10 mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and dried under high vacuum to give the title compound. MS: m/z=326 (M+1).

Intermediate 2



(±)-5'-Amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one

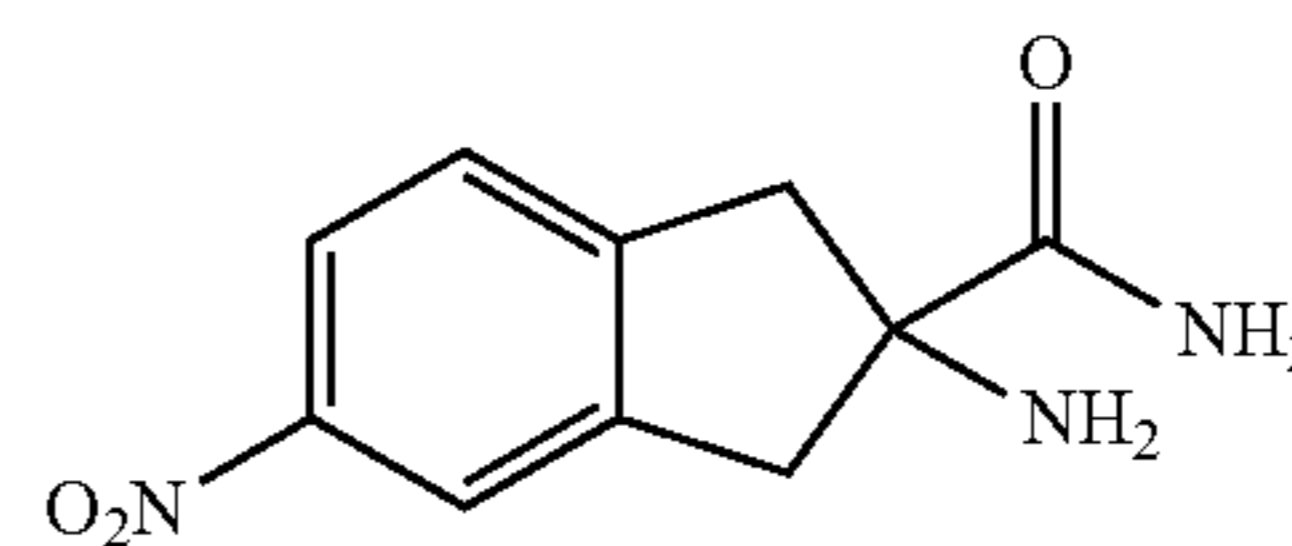
Step A. (±)-Benzyl(5-oxo-2-phenyl-1,1',3',5-tetrahydrospiro[imidazole-4,2'-inden]-5'-yl)carbamate

A solution of (±)-benzyl[2-amino-2-(aminocarbonyl)-2,3-dihydro-1H-inden-5-yl]carbamate (described in Intermediate 1, 35.0 mg, 0.108 mmol) and (trimethoxymethyl)benzene (0.022 mL, 0.129 mmol) in toluene (5 mL) was heated at reflux for 7.5 h. The reaction mixture was concentrated under reduced pressure. The crude product was dissolved in DMSO (1 mL) and purified by HPLC using a reversed phase C18 column and eluting with a gradient of H₂O:CH₃CN:CF₃CO₂H—90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined and concentrated to give the title compound. MS: m/z=412 (M+1).

Step B. (±)-5'-Amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one

To a solution of (±)-benzyl (5-oxo-2-phenyl-1,1',3',5-tetrahydrospiro[imidazole-4,2'-inden]-5'-yl)carbamate from Step A (568 mg, 1.94 mmol) in degassed MeOH (2 mL) was added 10% palladium on carbon (5 mg). The suspension was placed under a hydrogen balloon for 3 h, then filtered through a pad of Celite, concentrated, and dried under high vacuum to give the title compound. MS: m/z=278 (M+1).

Intermediate 3



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 (\pm) -2-Amino-5-nitroindane-2-carboxamideStep A. (\pm) -Di-tert-butyl 5'-nitro-2,5-dioxo-1',3'-dihydro-1H,3H-spiro[imidazolidine-4,2'-indene]-1,3-dicarboxylate

A solution of (\pm) -5'-nitro-1',3'-dihydro-2H,5H-spiro[imidazolidine-4,2'-indene]-2,5-dione (1.20 g, 4.85 mmol, described in Bell et al. (2006) *Bioorg. Med. Chem. Lett.* 16, 6165), di-tert-butyl dicarbonate (5.30 g, 24.3 mmol), TEA (540 mg, 5.34 mmol), and DMAP (12.0 mg, 0.097 mmol) in DME (29 mL) was stirred at ambient temperature for 16 h. The reaction mixture was concentrated in vacuo and the crude product dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with 10% HCl (20 mL), saturated Na_2CO_3 (20 mL), brine (20 mL), dried over Na_2SO_4 , filtered, concentrated and dried under high vacuum to give the title compound. MS: $m/z=448$ (M+1).

Step B. (\pm) -2-Amino-5-nitroindane-2-carboxylic acid

To a solution of (\pm) -di-tert-butyl 5'-nitro-2,5-dioxo-1',3'-dihydro-1H,3H-spiro[imidazolidine-4,2'-indene]-1,3-dicarboxylate from Step A (2.17 g, 4.85 mmol) in DME (16 mL) was added 1N NaOH (43.7 mL, 43.7 mmol) and the reaction mixture was stirred at ambient temperature for 20 h. The reaction mixture was diluted with water (20 mL) and Et_2O (20 mL). The suspension was filtered and the layers separated. The aqueous layer was further washed with Et_2O (20 mL). The aqueous layer was concentrated to a volume of 30 mL and purified by HPLC using a reversed phase C18 column and eluting with a gradient of $\text{H}_2\text{O}:\text{CH}_3\text{CN}:\text{CF}_3\text{CO}_2\text{H}$ —90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined and concentrated to give the title compound as the trifluoroacetate salt. MS: $m/z=223$ (M+1).

Step C. (\pm) -2-[(tert-Butoxycarbonyl)amino]-5-nitroindane-2-carboxylic acid

A solution of (\pm) -2-amino-5-nitroindane-2-carboxylic acid from Step B (490 mg, 1.46 mmol), di-tert-butyl dicarbonate (318 mg, 1.46 mmol), and TEA (0.609 mL, 4.37 mmol), was stirred in DME (20 mL) at ambient temperature for 24 h. At 20 h, additional di-tert-butyl dicarbonate (100 mg) was added. The reaction mixture was poured onto 10% HCl (30 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, concentrated and dried under high vacuum to give the title compound. MS: $m/z=323$ (M+1).

Step D. (\pm) -tert-Butyl[2-(aminocarbonyl)-5-nitro-2,3-dihydro-1H-inden-2-yl]carbamate A solution of (\pm) -2-[(tert-butoxycarbonyl)amino]-5-nitroindane-2-carboxylic acid from Step C (470 mg, 1.46 mmol), ammonium chloride (156 mg, 2.92 mmol), EDC (419 mg, 2.19 mmol), HORT (335 mg, 2.19 mmol), and DIEA (1.27 mL, 7.29 mmol) in DMF (5 mL) was stirred at ambient temperature for 16 h. The reaction mixture was poured onto saturated NaHCO_3 (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$ —100:0:0 to 90:9:1, to give the title compound. MS: $m/z=322$ (M+1).

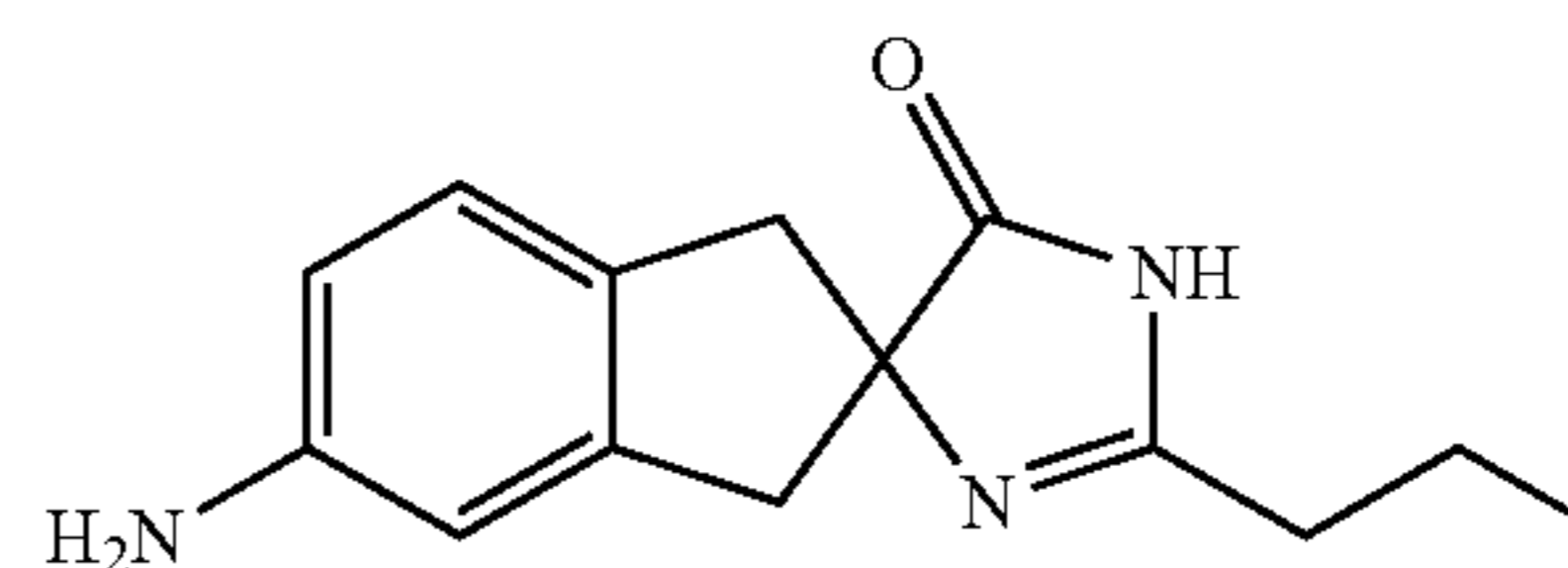
Step E. (\pm) -2-Amino-5-nitroindane-2-carboxamide

To a solution of (\pm) -tert-butyl[2-(aminocarbonyl)-5-nitro-2,3-dihydro-1H-inden-2-yl]carbamate from Step D (113 mg,

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0.352 mmol) in EtOAc (5 mL) was bubbled $\text{HCl}_{(g)}$ for 10 min. The reaction mixture was concentrated under reduced pressure. The crude product was dissolved in DMSO (1 mL) and purified by HPLC using a reversed phase C18 column and eluting with a gradient of $\text{H}_2\text{O}:\text{CH}_3\text{CN}:\text{CF}_3\text{CO}_2\text{H}$ —90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined and concentrated to give the title compound as the trifluoroacetate salt. MS: $m/z=258$ (M+1).

Intermediate 4

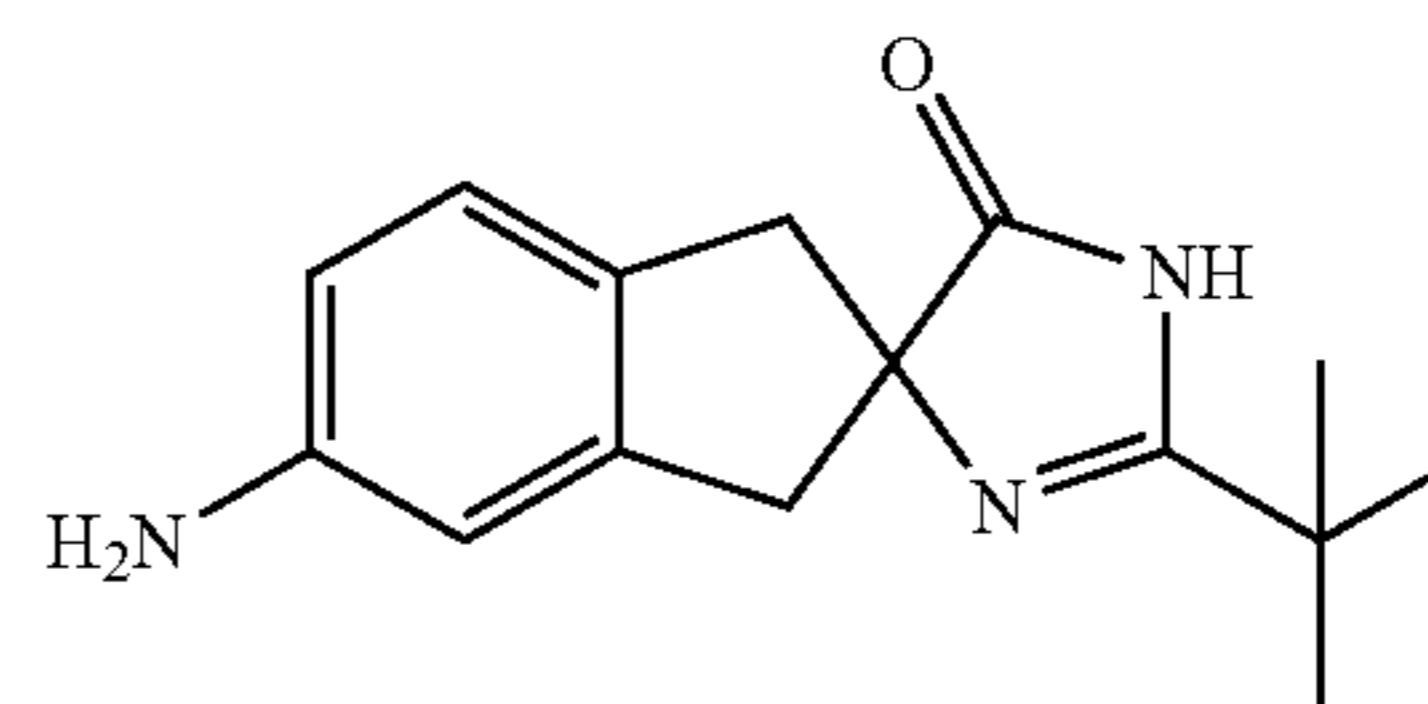
Step A. (\pm) -5'-Nitro-2-propyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one

A solution of (\pm) -2-amino-5-nitroindane-2-carboxamide, trifluoroacetate salt (described in Intermediate 3, 25.0 mg, 0.075 mmol) and 1,1,1-trimethoxybutane (0.060 mL, 0.373 mmol) in toluene (5 mL) was heated at reflux for 16 h. The reaction mixture was concentrated under reduced pressure to give the title compound. MS: $m/z=274$ (M+1).

Step B. (\pm) -5'-Amino-2-propyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one

To a solution of (\pm) -5'-nitro-2-propyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one from Step A (20.0 mg, 0.073 mmol) in degassed MeOH (5 mL) was added 10% palladium on carbon (10 mg). The suspension was placed under a hydrogen balloon for 1 h, then filtered through a pad of Celite, concentrated, and dried under high vacuum to give the title compound. MS: $m/z=244$ (M+1).

Intermediate 5

 (\pm) -5'-Amino-2-tert-butyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-oneStep A. (\pm) -2-[(2,2-Dimethylpropanoyl)amino]-5-nitroindane-2-carboxamide

A solution of (\pm) -2-amino-5-nitroindane-2-carboxamide, trifluoroacetate salt (described in Intermediate 3, 25.0 mg, 0.075 mmol), 2,2-dimethylpropanoyl chloride (0.011 mL, 0.089 mmol), and triethylamine (0.026 mL, 0.186 mmol) in THF (5 mL) was stirred at ambient temperature for 16 h. The reaction mixture was poured onto saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). A solid precipitate

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was filtered and collected, then dissolved in MeOH and combined with the organic layers. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound. MS: m/z=306 (M+1).

Step B. (±)-2-tert-Butyl-5'-nitro-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one A solution of (±)-2-[(2,2-dimethylpropanoyl)amino]-5-nitroindane-2-carboxamide from Step A (23.0 mg, 0.075 mmol) and 5N NaOH (0.075 mL, 0.38 mmol) in EtOH (5 mL) was heated to reflux for 3.5 h. The reaction mixture was poured onto saturated NH₄Cl (10 mL) and extracted with CH₂Cl₂ (3×10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound. MS: m/z=288 (M+1).

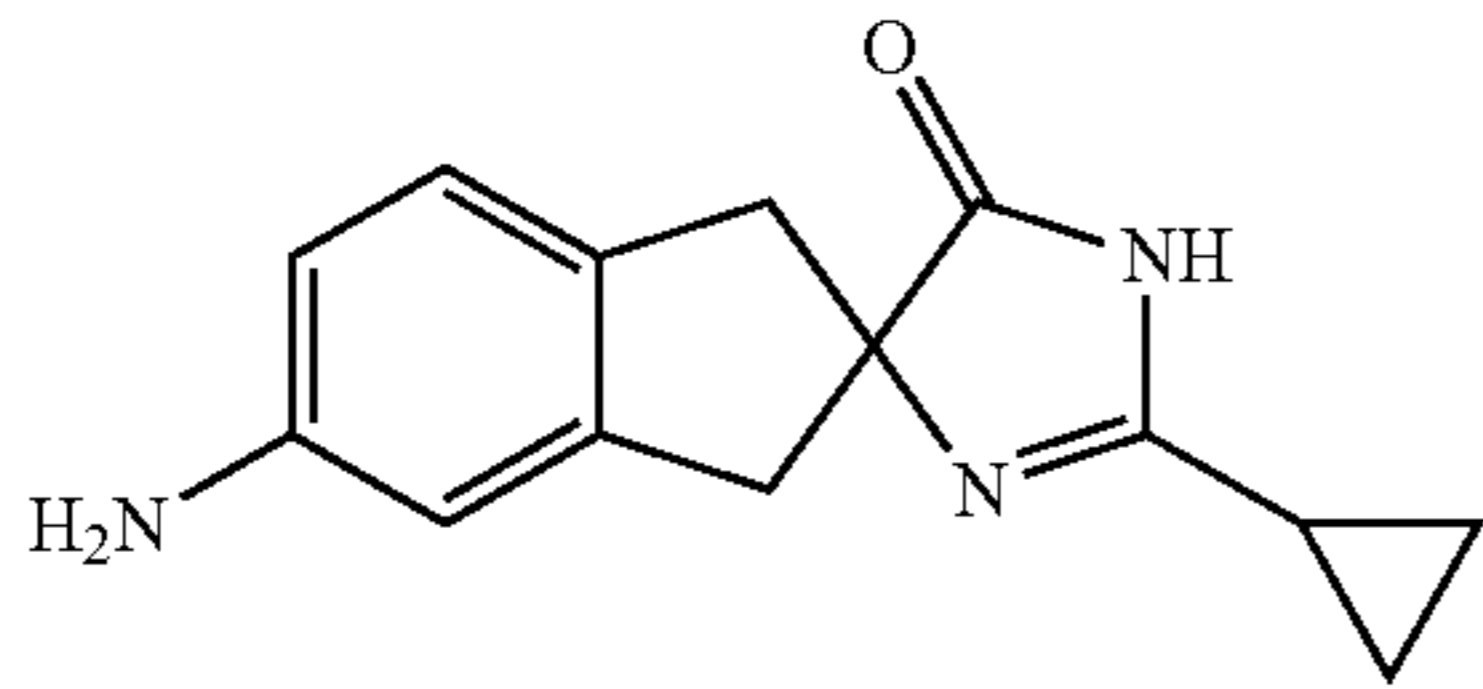
Step C, (±)-5'-Amino-2-tert-butyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one

To a solution of (±)-2-tert-butyl-5'-nitro-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one from Step B (22.0 mg, 0.077 mmol) in degassed MeOH (5 mL) was added 10% palladium on carbon (10 mg). The suspension was placed under a hydrogen balloon for 1 h, then filtered through a pad of Celite, concentrated, and dried under high vacuum to give the title compound. MS: m/z=258 (M+1).

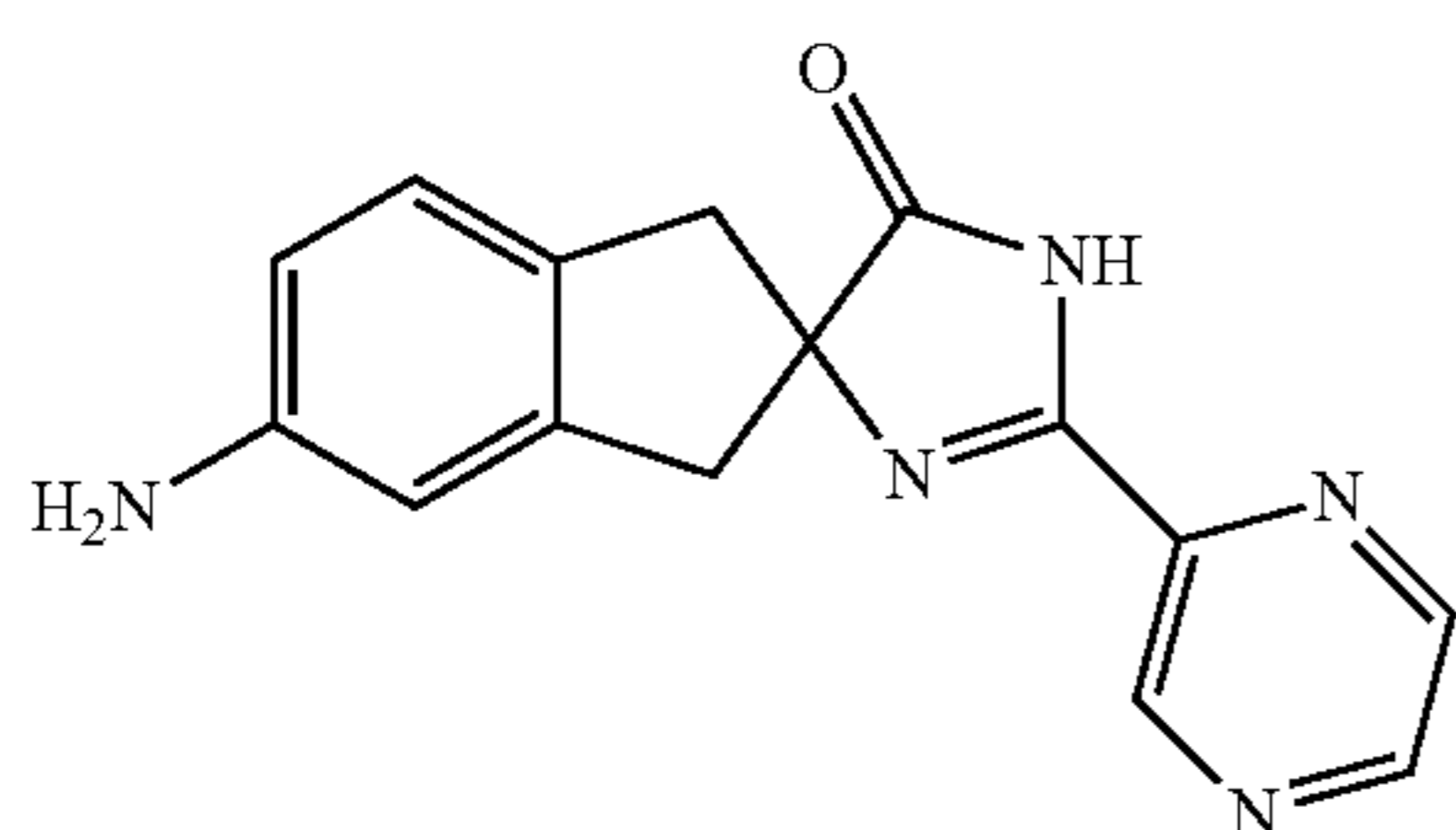
Intermediate 6

Essentially following the procedures outlined for Intermediate 5 the compound listed in Table 1 was prepared. The requisite starting materials were commercially available, described in the literature, synthesized according to methodology described herein (vide supra), or readily synthesized by one skilled in the art of organic synthesis.

TABLE 1

Example	R ^b	MS (M + 1)
6		242

Intermediate 7



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(±)-5'-Amino-2-pyrazin-2-yl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one

Step A. (±)-Benzyl{2-(aminocarbonyl)-2-[(pyrazin-2-ylcarbonyl)amino]-2,3-dihydro-1H-inden-5-yl}carbamate

A solution of (±)-benzyl[2-amino-2-(aminocarbonyl)-2,3-dihydro-1H-inden-5-yl]carbamate (described in Intermediate 1, 52.0 mg, 0.118 mmol), pyrazine-2-carboxylic acid (15.0 mg, 0.118 mmol), EDC (34.0 mg, 0.178 mmol), HOBT (27.0 mg, 0.178 mmol), and triethylamine (0.103 mL, 0.592 mmol) in DMF (5 mL) was stirred at ambient temperature for 16 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H₂O:CH₃CN:CF₃CO₂H-90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined and concentrated to give the title compound as the trifluoroacetate salt. MS: m/z=432 (M+1).

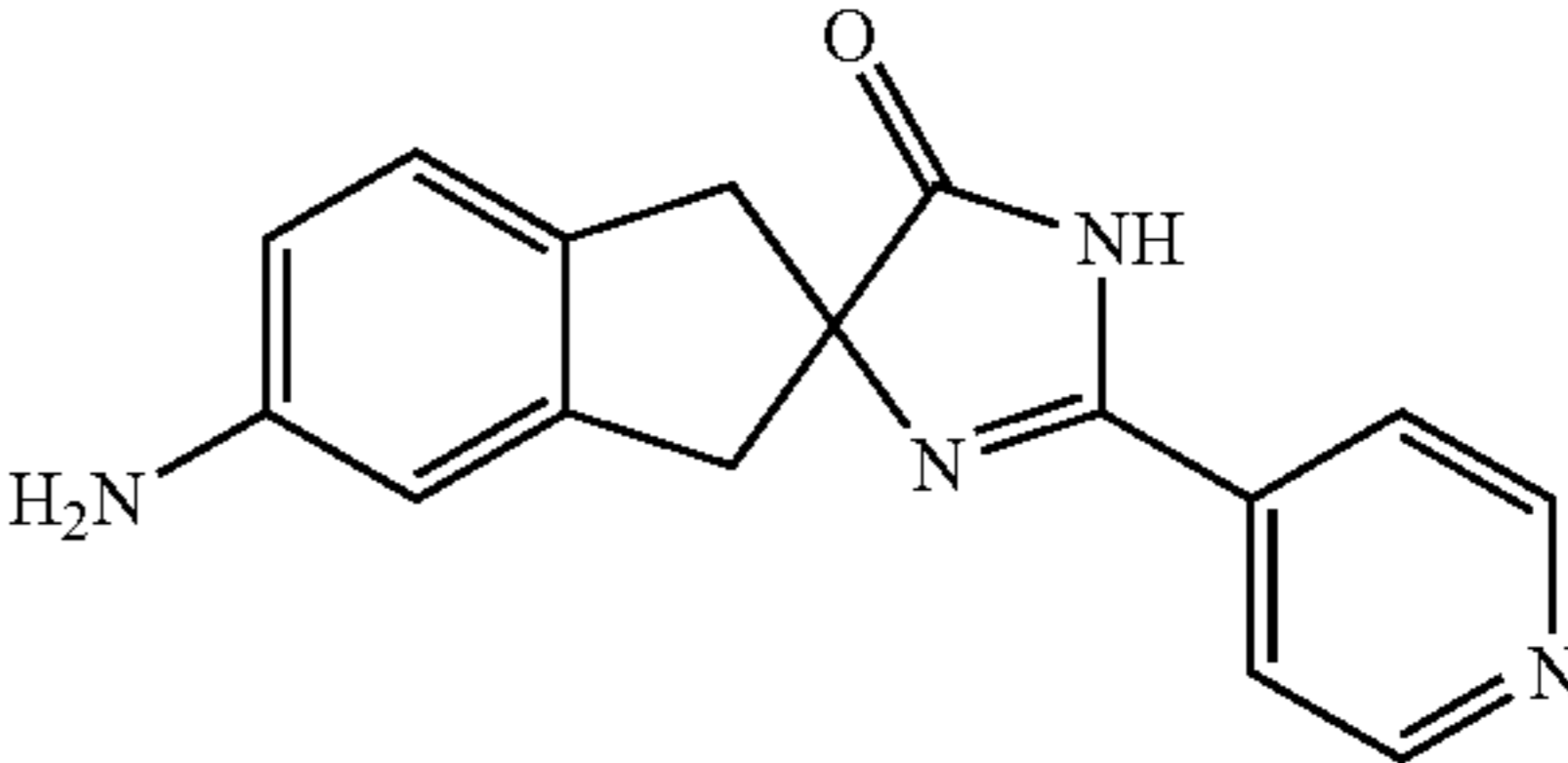
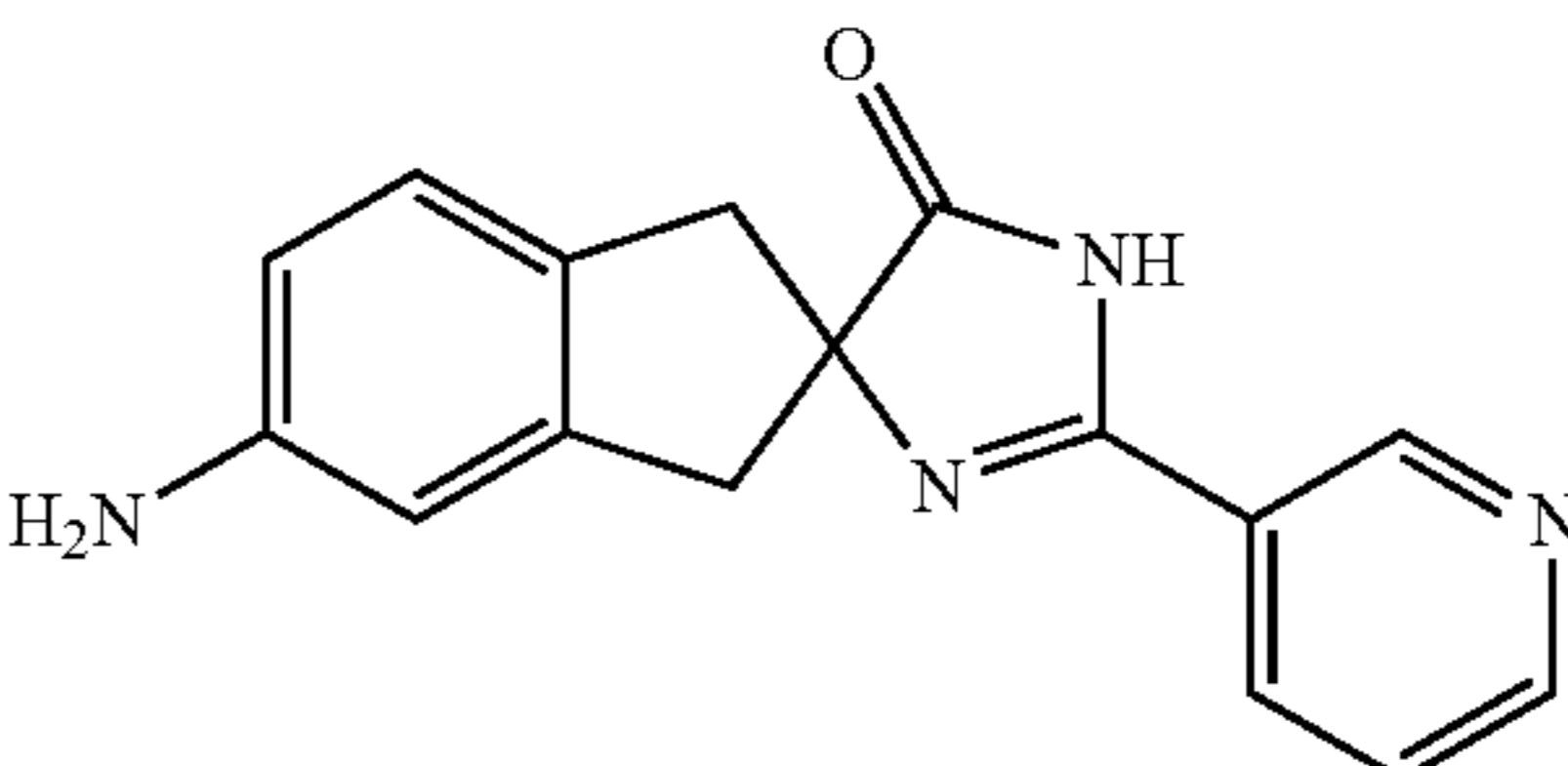
Step B. (±)-5'-Amino-2-pyrazin-2-yl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one

A solution of (±)-benzyl{2-(aminocarbonyl)-2-[(pyrazin-2-ylcarbonyl)amino]-2,3-dihydro-1H-inden-5-yl}carbamate from Step A (58.0 mg, 0.106 mmol) and 5N NaOH (0.106 mL, 0.532 mmol) in EtOH (5 mL) was heated to reflux for 5 h. The reaction mixture was concentrated under reduced pressure. The crude product was dissolved in DMSO (1 mL) and purified by HPLC using a reversed phase C18 column and eluting with a gradient of H₂O:CH₃CN:CF₃CO₂H-90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined and concentrated to give the title compound as the trifluoroacetate salt. MS: m/z=280 (M+1).

Intermediates 8-10

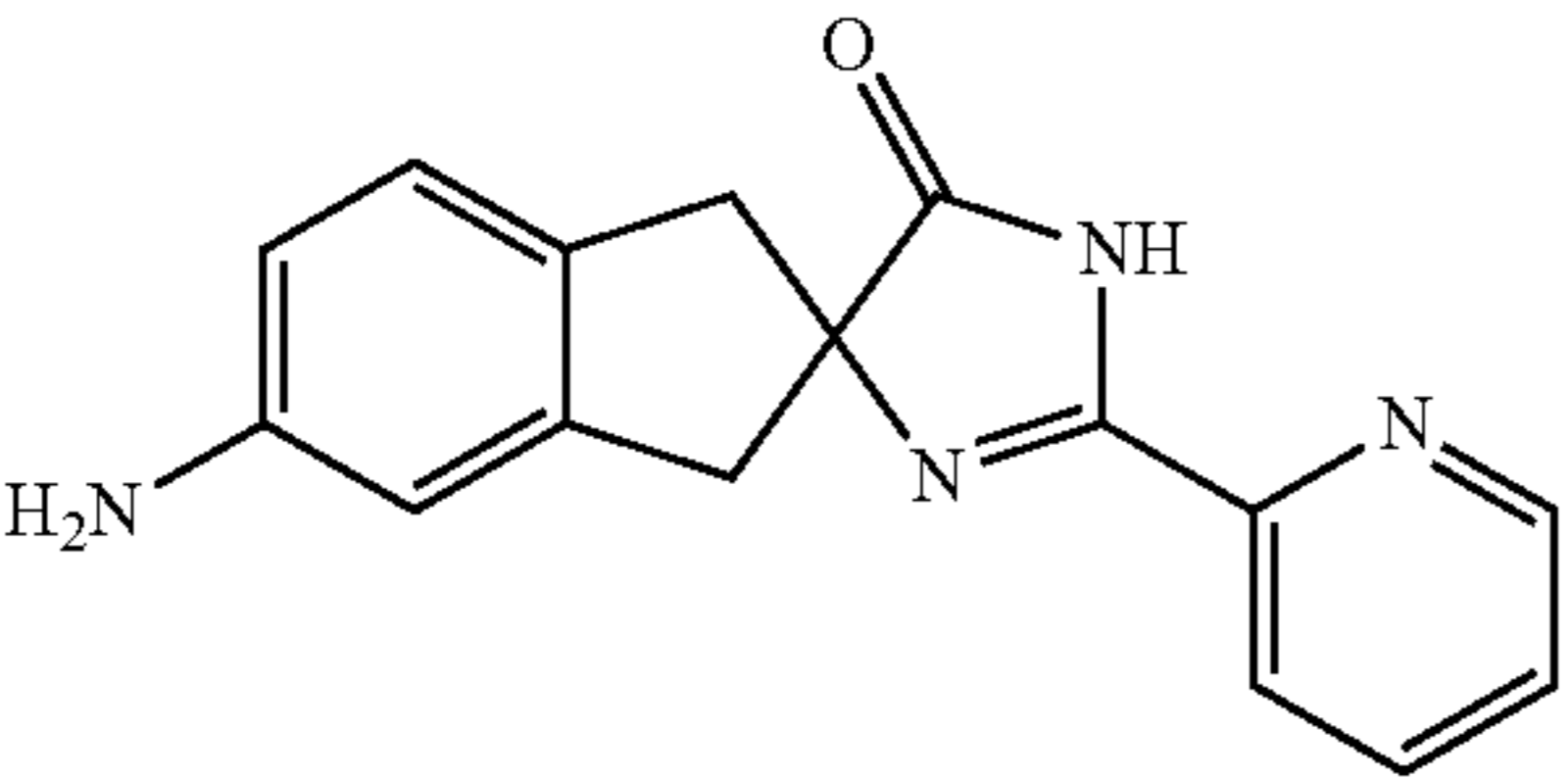
Essentially following the procedures outlined for Intermediate 4 the compound listed in Table 1 was prepared. The requisite starting materials were commercially available, described in the literature, synthesized according to methodology described herein (vide supra), or readily synthesized by one skilled in the art of organic synthesis.

TABLE 2

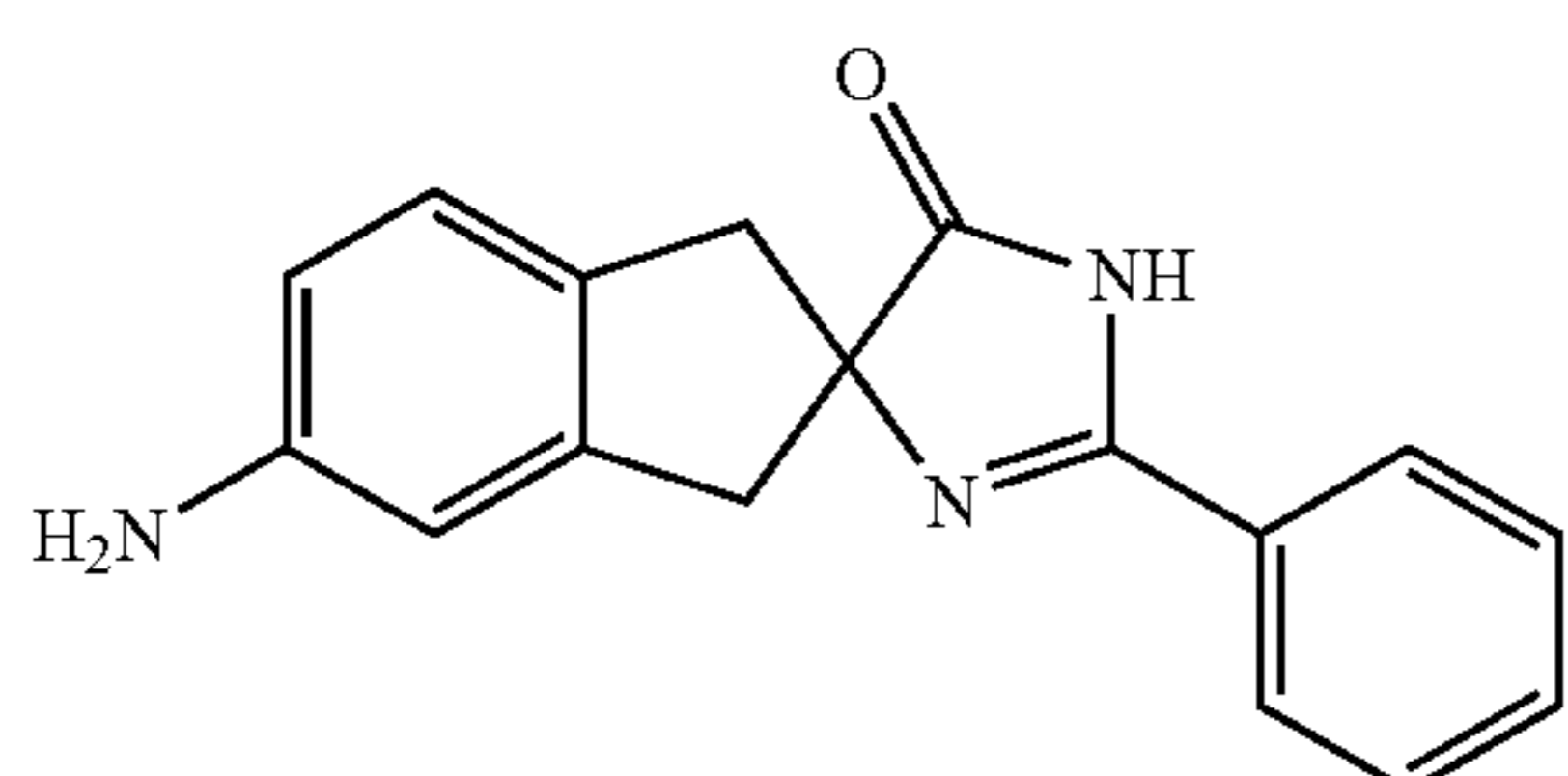
Example	R ^b	MS (M + 1)
8		279
9		279

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TABLE 2-continued

Example	R ^b	MS (M+1)
10		279

Intermediate 11

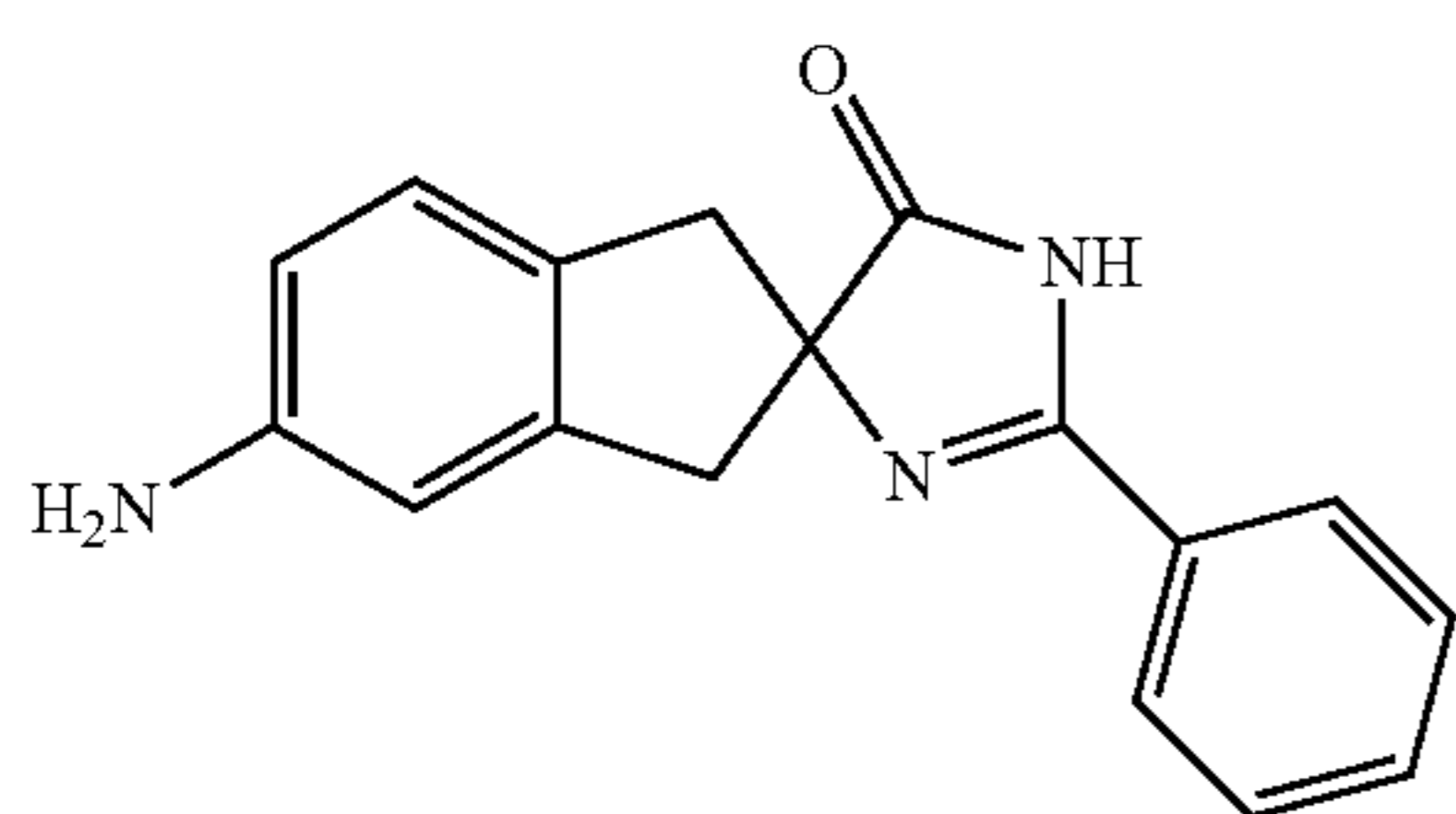


5'-Amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one, enantiomer A

Step A. (±)-Benzyl(5-oxo-2-phenyl-1,1',3',5-tetrahydrospiro[imidazole-4,2'-inden]-5'-yl)carbamate

The enantiomers of (±)-5'-amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one (described in Intermediate 2, 35.0 mg, 0.108 mmol) were resolved using a Chiralcel OJ-H column and eluting with heptanes:EtOH-40:60 with 0.1% DEA as a modifier. The first major peak to elute was the title compound, 5'-amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one, enantiomer A. MS: m/z=278 (M+1).

Intermediate 11



5'-Amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one, enantiomer B

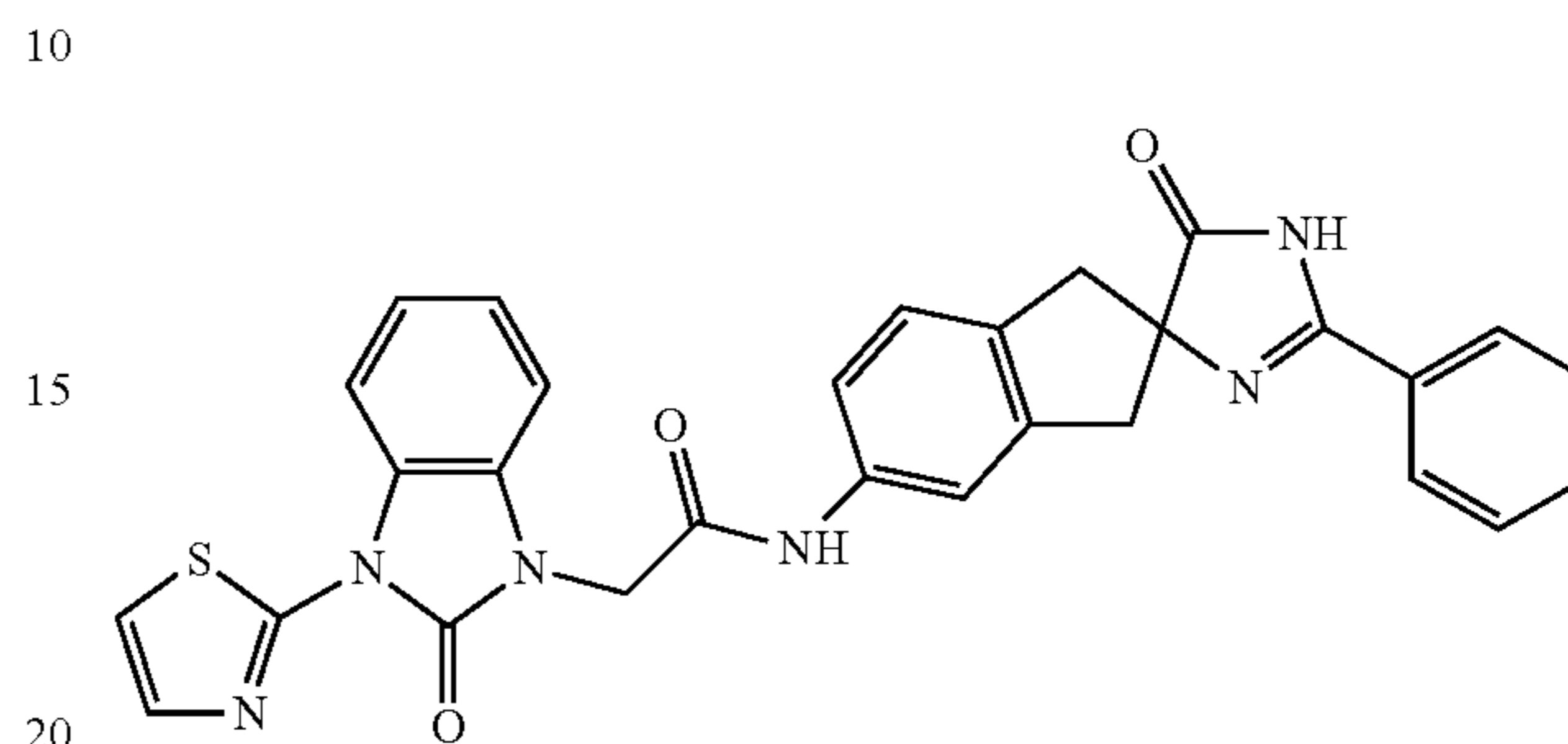
Step A. (±)-Benzyl(5-oxo-2-phenyl-1,1',3',5-tetrahydrospiro[imidazole-4,2'-inden]-5'-yl)carbamate

The enantiomers of (±)-5'-amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one (described in Intermediate 2, 35.0 mg, 0.108 mmol) were resolved using a

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Chiralcel OJ-H column and eluting with heptanes:EtOH-40:60 with 0.1% DEA as a modifier. The second major peak to elute was the title compound, 5'-amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one, enantiomer B. MS: m/z=278 (M+1).

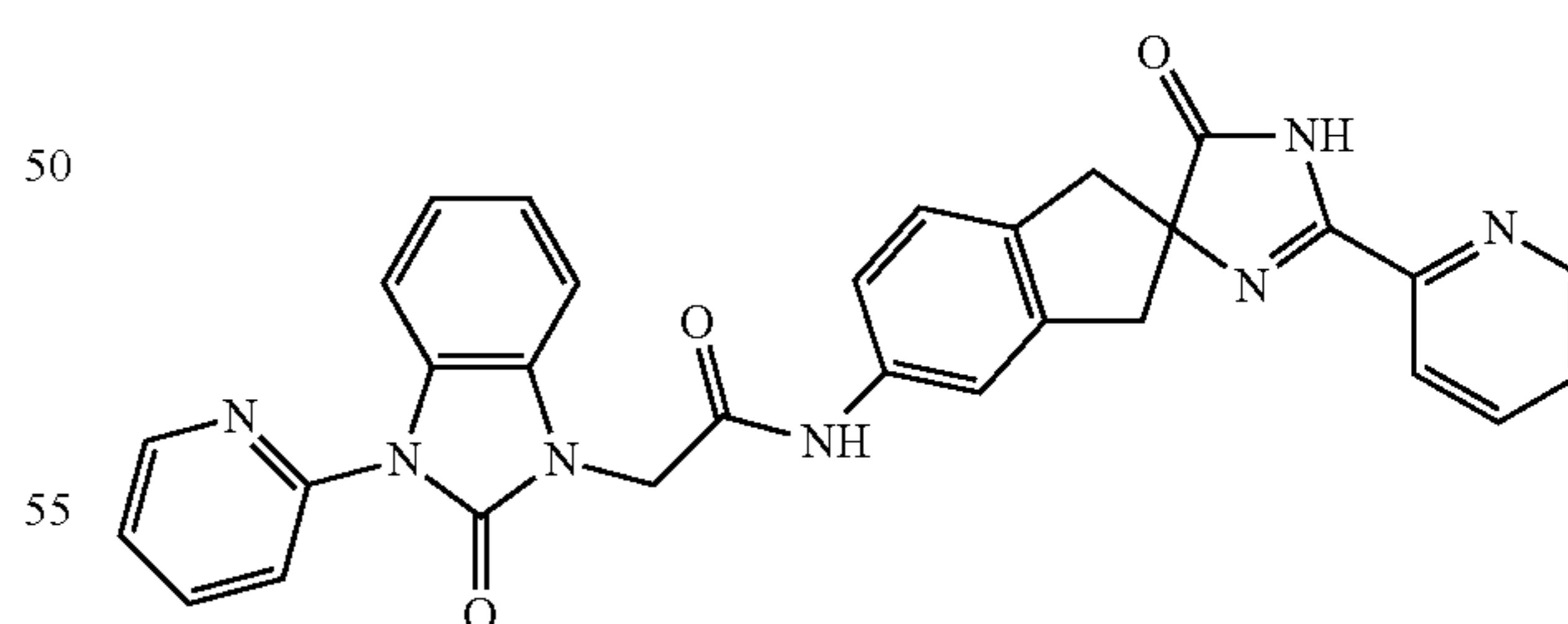
EXAMPLE 1



(±)-N-(5-oxo-2-phenyl-1,1',3',5-tetrahydrospiro[imidazole-4,2'-inden]-5'-yl)-2-[2-oxo-3-(1,3-thiazol-2-yl)-2,3-dihydro-1H-benzimidazol-1-yl]acetamide

A mixture of (±)-5'-amino-2-phenyl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one (10 mg, 0.036 mmol, described in Intermediate 2), [2-oxo-3-(1,3-thiazol-2-yl)-2,3-dihydro-1H-benzimidazol-1-yl]acetic acid (10 mg, 0.036 mmol) [Bell et al U.S. Pat. No. 7,202,251], EDC (10 mg, 0.054 mmol), HOBT (8.0 mg, 0.054 mmol), and N,N-diisopropylethylamine (0.031 mL, 0.180 mmol) was stirred in DMF (1 mL) at ambient temperature for 24 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H₂O:CH₃CN:CF₃CO₂H-90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined and concentrated to give the title compound as the trifluoroacetate salt. MS: m/z=535 (M+1). HRMS: m/z=535.1559; calculated m/z=535.1547 for C₂₉H₂₂N₆O₃S₁.

EXAMPLE 2



(±)-2-(2-oxo-3-pyridin-2-yl-2,3-dihydro-1H-benzimidazol-1-yl)-N-(5-oxo-2-pyridin-2-yl-1,1',3',5-tetrahydrospiro[imidazole-4,2'-inden]-5'-yl)acetamide

A mixture of (±)-5'-amino-2-pyridin-2-yl-1',3'-dihydrospiro[imidazole-4,2'-inden]-5(1H)-one, bis-trifluoroacetate salt (26 mg, 0.051 mmol, described in Intermediate 10),

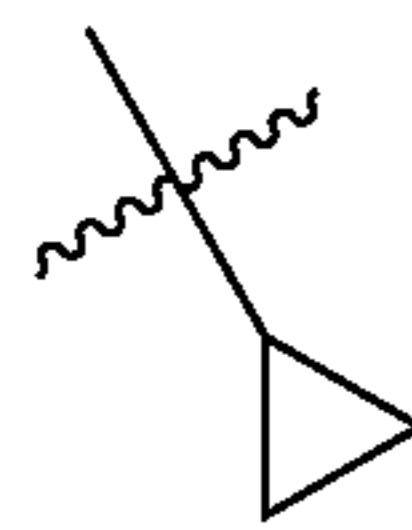
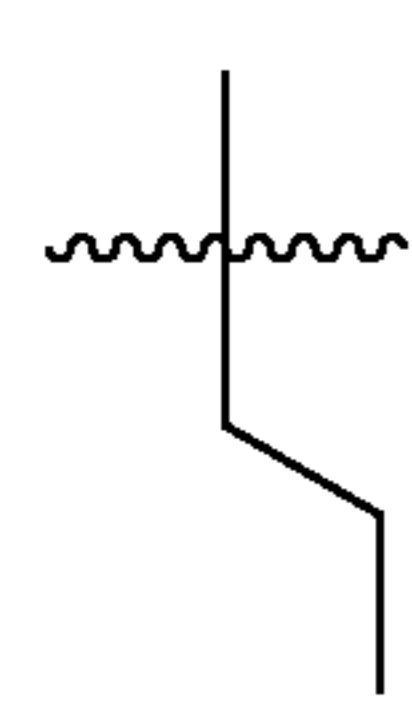
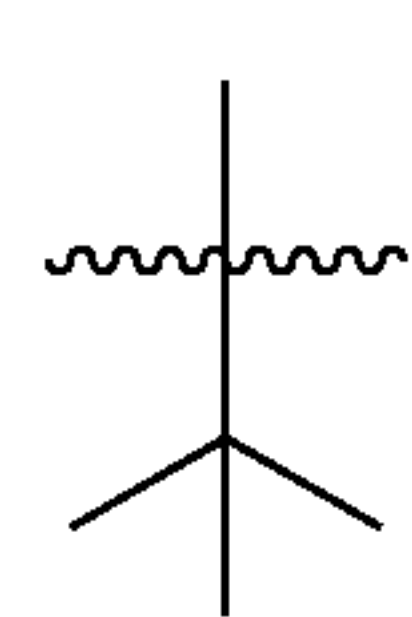
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(2-oxo-3-pyridin-2-yl-2,3-dihydro-1H-benzimidazol-1-yl) acetic acid (15 mg, 0.056 mmol) [Bell et al. (2006) *Bioorg. Med. Chem. Lett.* 16, 6165], EDC (15 mg, 0.077 mmol), HOBT (12 mg, 0.077 mmol), and N,N-diisopropylethylamine (0.045 mL, 0.26 mmol) was stirred in DMF (0.5 mL) at ambient temperature for 72 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H₂O:CH₃CN:CF₃CO₂H-90:10:0.1 to 5:95:0.1. The pure, product-containing fractions were combined and concentrated to give the title compound as the trifluoroacetate salt. MS: m/z=530 (M+1). HRMS: m/z=530.1953; calculated m/z=530.1935 for C₃₀H₂₃N₇O₃.

EXAMPLES 3-9

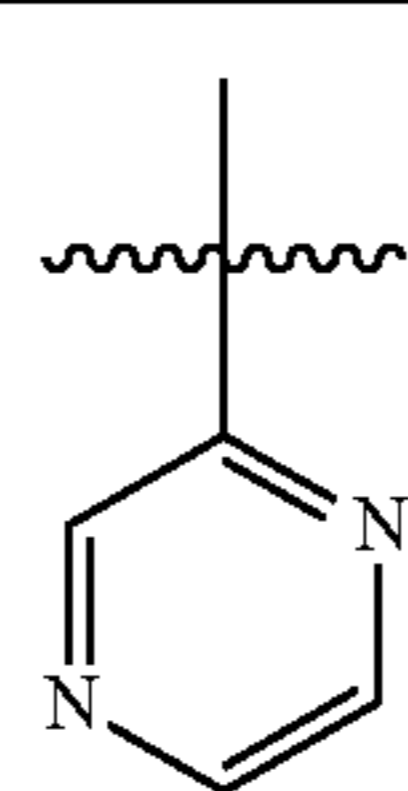
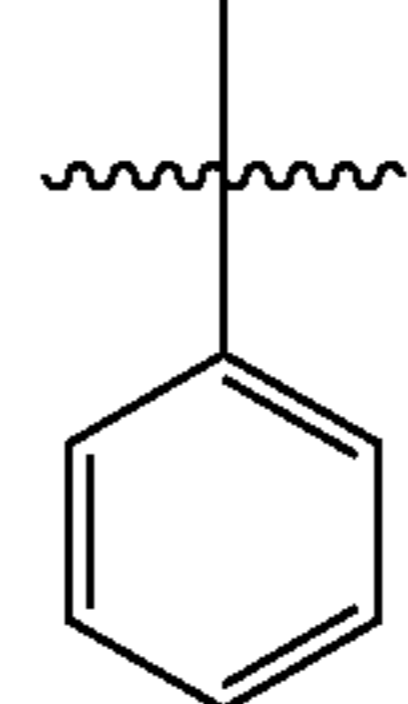
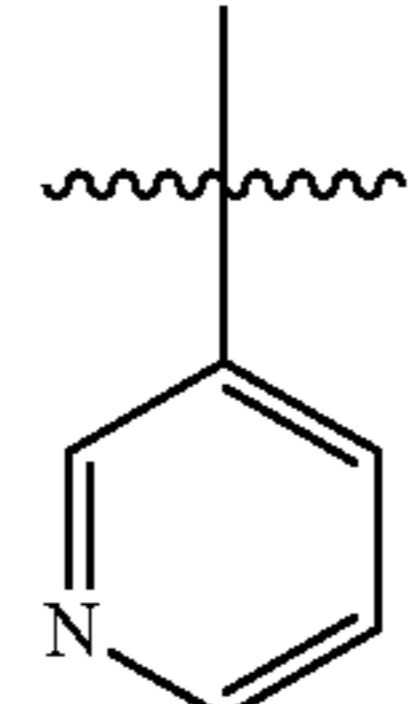
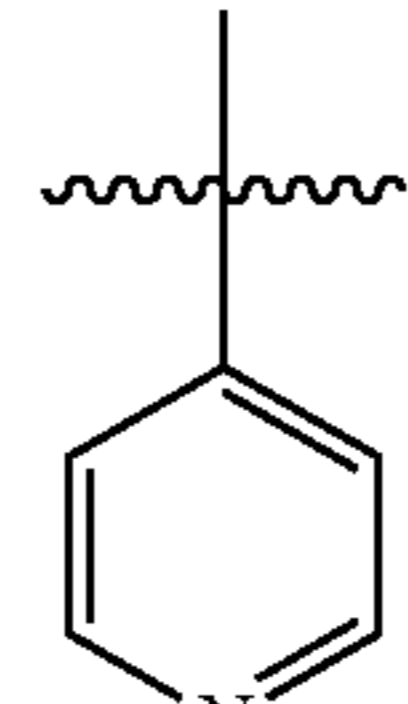
Essentially following the procedures outlined for Example 1 the compounds listed in Table 3 were prepared. The requisite starting materials were commercially available, described in the literature, synthesized according to methodology described herein (vide supra), or readily synthesized by one skilled in the art of organic synthesis. In some cases, straightforward protecting group strategies were applied.

TABLE 3

Example	R	MS (M + 1)	Intermediate
3		493	6
4		495	4
5		509	5

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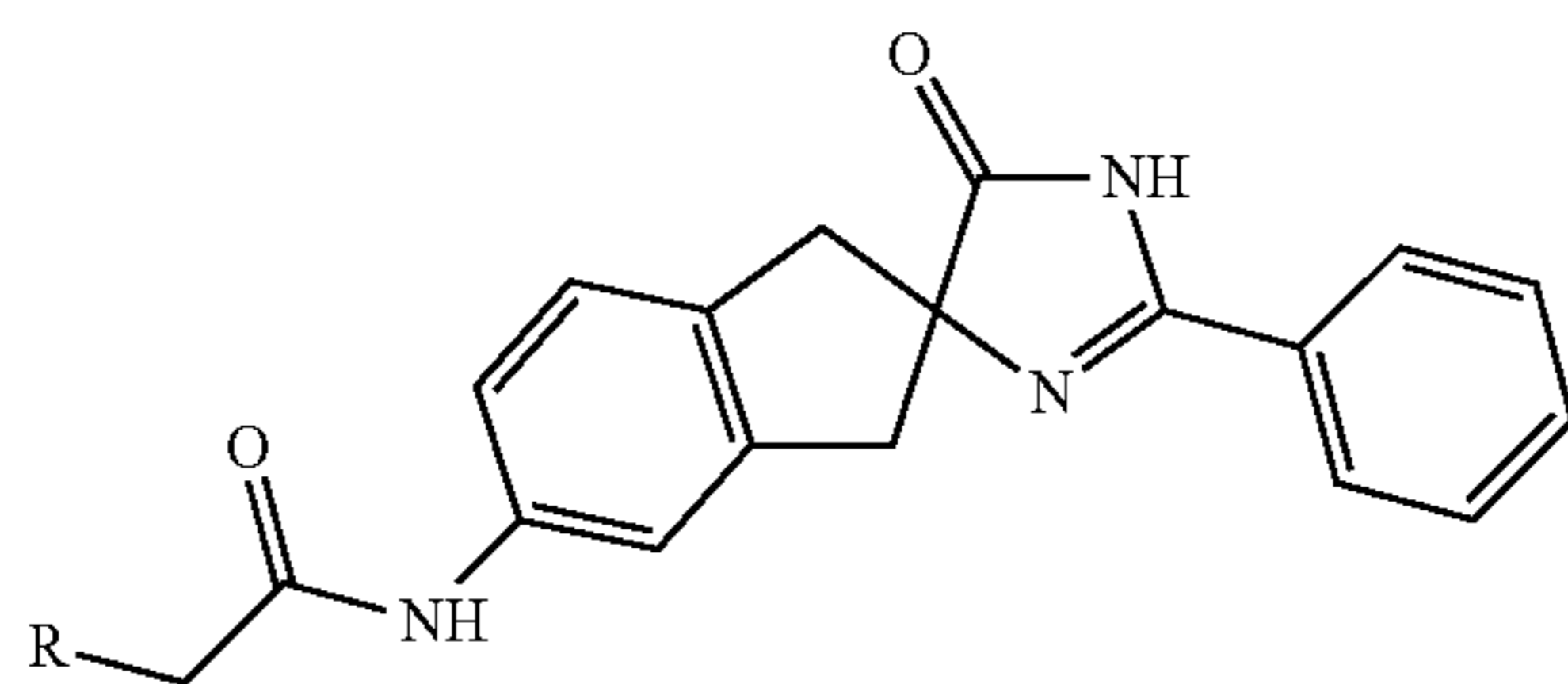
TABLE 3-continued

Example	R	MS (M + 1)	Intermediate
6		531	7
7		529	2
8		530	9
9		530	8

EXAMPLES 10-15

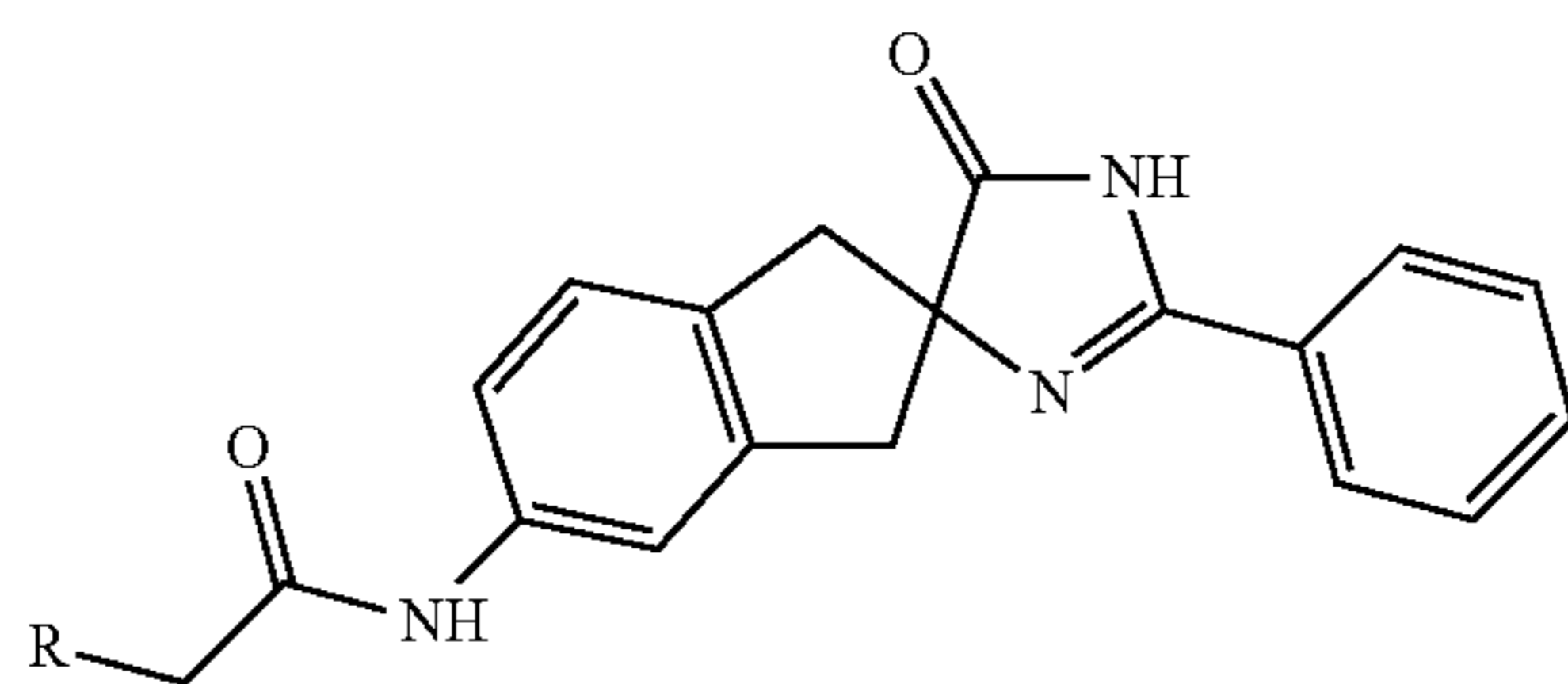
Essentially following the procedures outlined for Example 1 the compounds listed in Table 4 were prepared. The requisite starting materials were commercially available, described in the literature, synthesized according to methodology described herein (vide supra), or readily synthesized by one skilled in the art of organic synthesis. In some cases, straightforward protecting group strategies were applied.

TABLE 4



Example	R	MS (M + 1)	Amine Intermediate	R-Literature Reference
10	<p>racemic</p>	584	2	WO 2008/020902
11	<p>diastereomer A</p>	584	11	WO 2008/020902
12	<p>diastereomer B</p>	584	12	WO 2008/020902

TABLE 4-continued

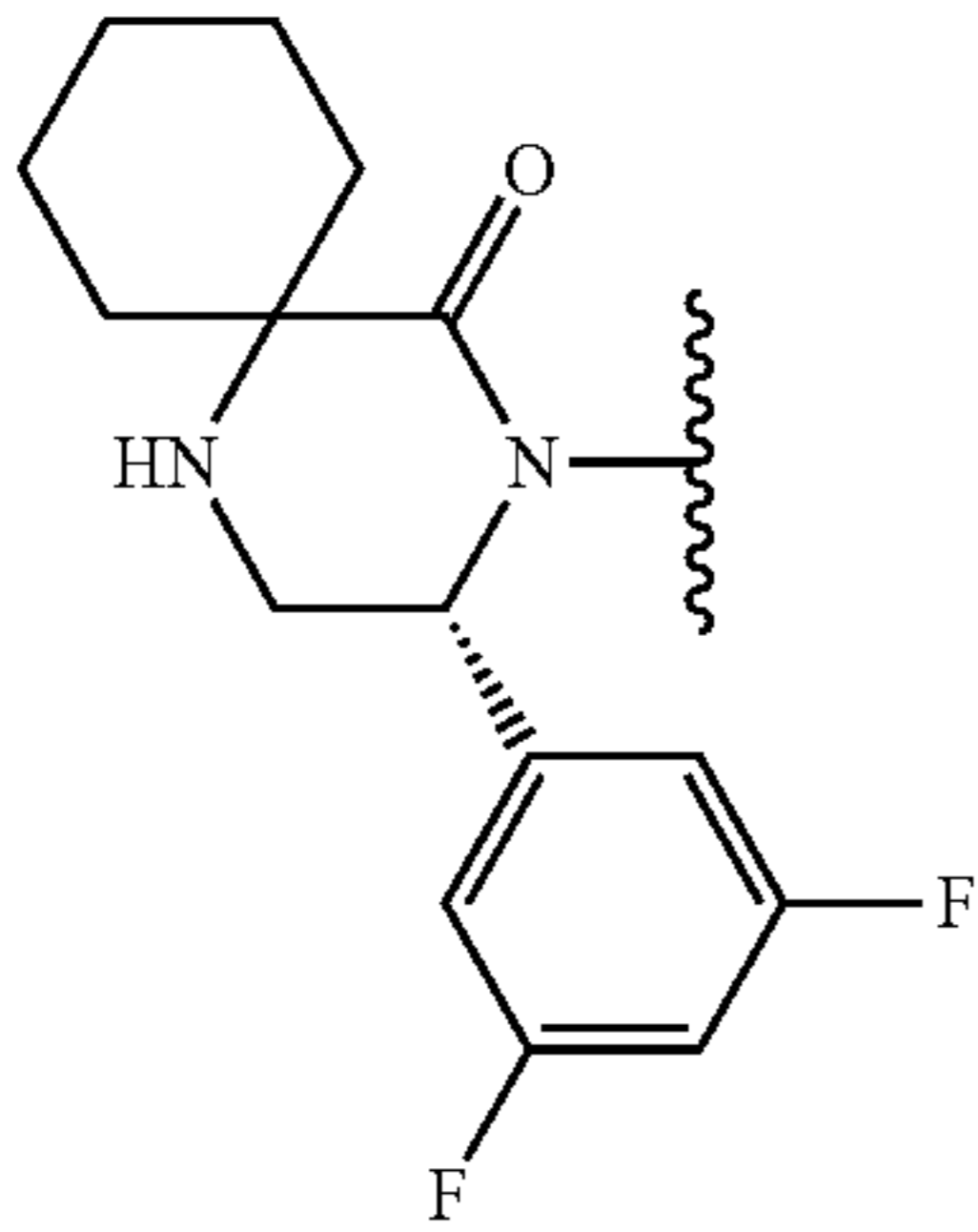
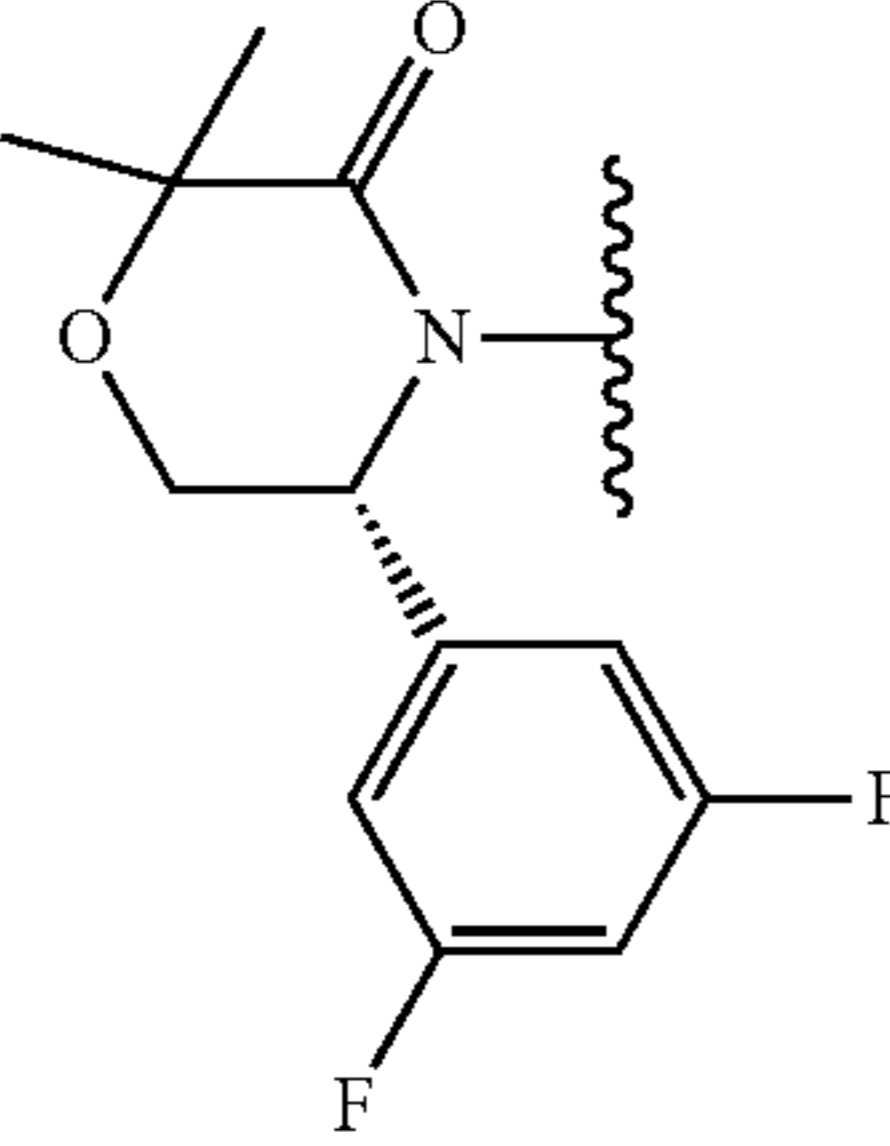
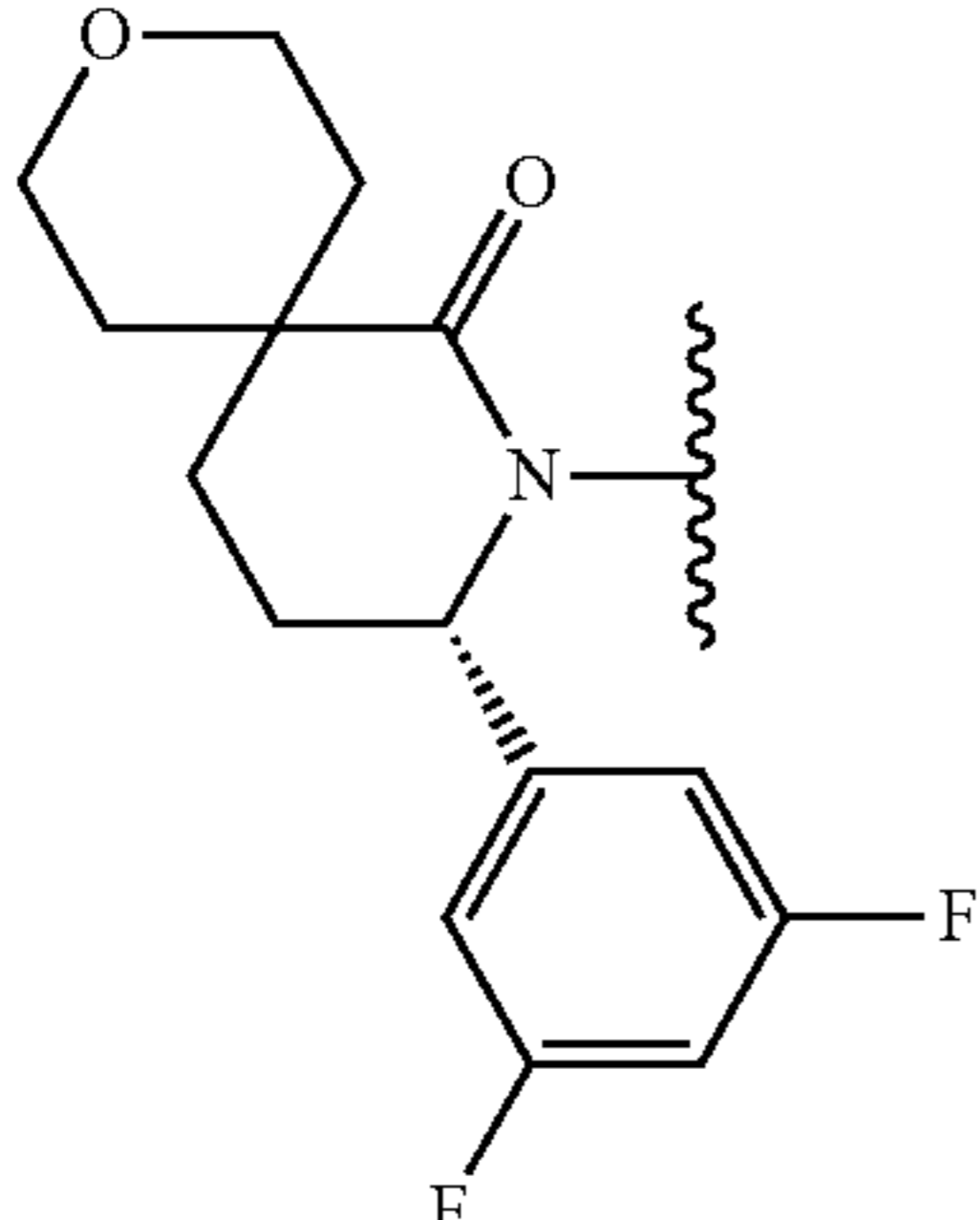


Example	R	MS (M + 1)	Amine Intermediate	R-Literature Reference
13		598	2	WO 2008/020902
14		583	2	WO 2008/020902
15		597	11	WO 2008/020902

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EXAMPLES 16-19

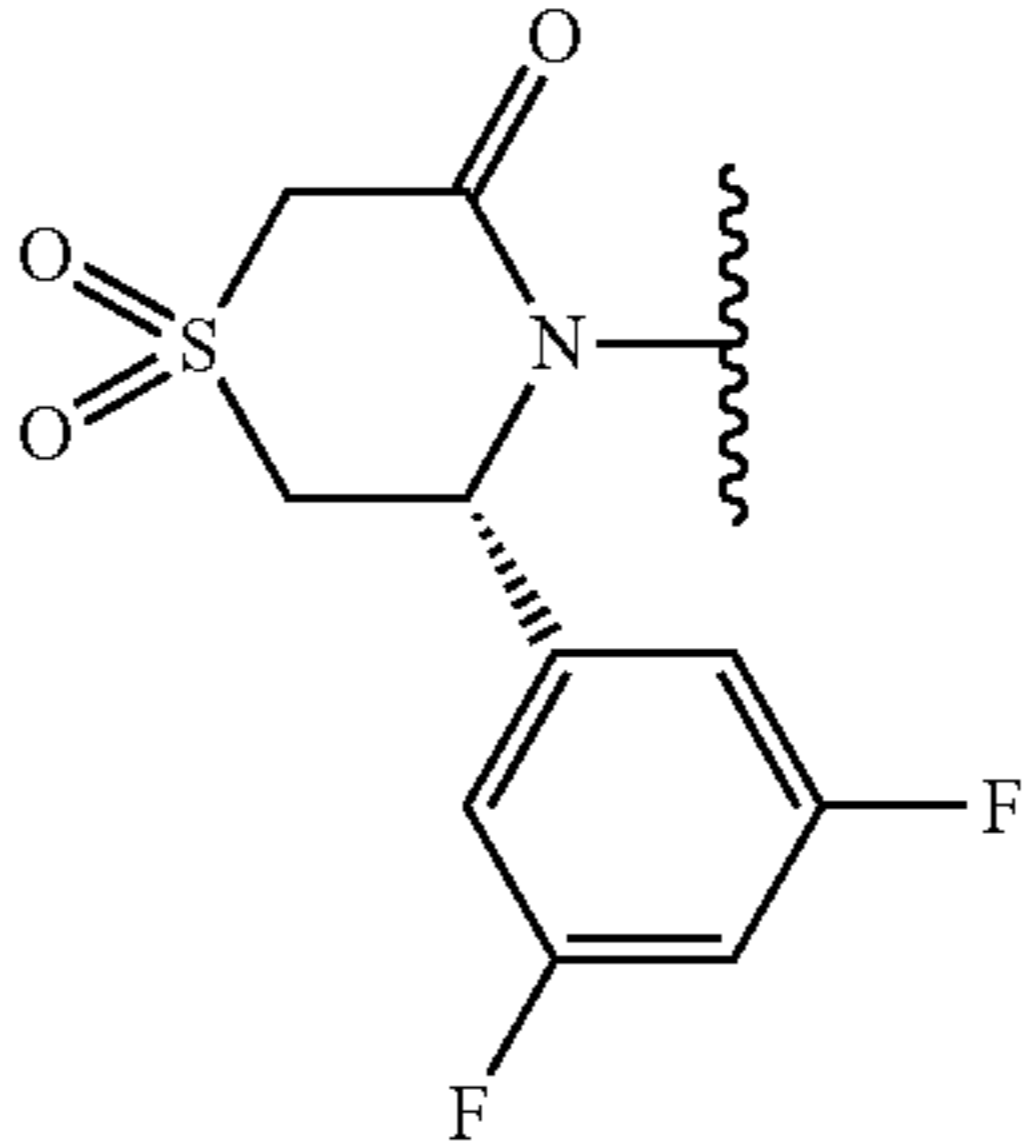
Essentially following the procedures outlined for Example 1 the compounds listed in Table 5 are prepared. The requisite starting materials are commercially available, described in the literature referenced below, synthesized according to methodology described herein (vide supra), or readily synthesized by one skilled in the art of organic synthesis. In some cases, straightforward protecting group strategies are applied.

TABLE 5

Example	R	Literature Reference
16		WO 2008/020902
17		WO 2008/020902
18		WO 2008/020902

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TABLE 5-continued

Example	R	Literature Reference
19		WO 2008/020902

Although specific enantiomers and diastereomers appear in the above Examples and Intermediates, it is well understood by those skilled in the art that modifications to reaction conditions and reagents (for example, but not limited to: using the opposite chirality for starting materials; different catalysts; using the opposite chirality for reagents; choosing to use a different enantiomer or diastereomer subsequent to a chiral resolution) will provide alternative enantiomers and diastereomers, all of which are included in the spirit and scope of the invention. It is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

The utility of the compounds in accordance with the present invention as antagonists of CGRP receptor activity may be demonstrated by methodology known in the art. Inhibition of the binding of ^{125}I -CGRP to receptors and functional antagonism of CGRP receptors were determined as follows:

NATIVE RECEPTOR BINDING ASSAY: The binding of ^{125}I -CGRP to receptors in SK-N-MC cell membranes was carried out essentially as described (Edvinsson et al. (2001) *Eur. J. Pharmacol.* 415, 39-44). Briefly, membranes (25 μg) were incubated in 1 mL of binding buffer [10 mM HEPES, pH 7.4, 5 mM MgCl_2 and 0.2% bovine serum albumin (BSA)] containing 10 pM ^{125}I -CGRP and antagonist. After incubation at room temperature for 3 h, the assay was terminated by filtration through GFB glass fibre filter plates (PerkinElmer) that had been blocked with 0.5% polyethyleneimine for 3 h. The filters were washed three times with ice-cold assay buffer (10 mM HEPES, pH 7.4 and 5 mM MgCl_2), then the plates were air dried. Scintillation fluid (50 μL) was added and the radioactivity was counted on a Topcount (Packard Instrument). Data analysis was carried out by using Prism and the K_i was determined by using the Cheng-Prusoff equation (Cheng & Prusoff (1973) *Biochem. Pharmacol.* 22, 3099-3108).

RECOMBINANT RECEPTOR: Human CL receptor (Genbank accession number L76380) was subcloned into the expression vector pIRESHyg2 (BD Biosciences Clontech) as a 5'NheI and 3' PmeI fragment. Human RAMP1 (Genbank accession number AJ001014) was subcloned into the expression vector pIRESpuro2 (BD Biosciences Clontech) as a 5'NheI and 3'NotI fragment. HEK 293 cells (human embryonic kidney cells; ATCC #CRL-1573) were cultured in DMEM with 4.5 g/L glucose, 1 mM sodium pyruvate and 2 mM glutamine supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin and 100 µg/mL streptomycin, and maintained at 37° C. and 95% humidity. Cells were subcultured by treatment with 0.25% trypsin with 0.1% EDTA in HBSS. Stable cell line generation was accomplished by co-transfecting 10 µg of DNA with 30 µg Lipofectamine 2000 (Invitrogen) in 75 cm² flasks. CL receptor and RAMP1 expression constructs were co-transfected in equal amounts. Twenty-four hours after transfection the cells were diluted and selective medium (growth medium+300 µg/mL hygromycin and 1 µg/mL puromycin) was added the following day. A clonal cell line was generated by single cell deposition utilizing a FACS Vantage SE (Becton Dickinson). Growth medium was adjusted to 150 µg/mL hygromycin and 0.5 µg/mL puromycin for cell propagation.

RECOMBINANT RECEPTOR BINDING ASSAY: Cells expressing recombinant human CL receptor/RAMP1 were washed with PBS and harvested in harvest buffer containing 50 mM HEPES, 1 mM EDTA and Complete protease inhibitors (Roche). The cell suspension was disrupted with a laboratory homogenizer and centrifuged at 48,000 g to isolate membranes. The pellets were resuspended in harvest buffer plus 250 mM sucrose and stored at -70° C. For binding assays, 20 µg of membranes were incubated in 1 ml binding buffer (10 mM HEPES, pH 7.4, 5 mM MgCl₂, and 0.2% BSA) for 3 hours at room temperature containing 10 pM ¹²⁵I-hCGRP (GE Healthcare) and antagonist. The assay was terminated by filtration through 96-well GFB glass fiber filter plates (PerkinElmer) that had been blocked with 0.05% polyethyleneimine. The filters were washed 3 times with ice-cold assay buffer (10 mM HEPES, pH 7.4 and 5 mM MgCl₂). Scintillation fluid was added and the plates were counted on a Topcount (Packard). Non-specific binding was determined and the data analysis was carried out with the apparent dissociation constant (K_i) determined by using a non-linear least squares fitting the bound CPM data to the equation below:

$$Y_{obsd} = \frac{(Y_{max} - Y_{min})(\% I_{max} - \% I_{min}/100) + Y_{min} + (Y_{max} - Y_{min})(100 - \% I_{max}/100)}{1 + ([Drug]/K_i)(1 + [Radiolabel]/K_d)^{nH}}$$

Where Y is observed CPM bound, Y_{max} is total bound counts, Y_{min} is non specific bound counts, (Y_{max}-Y_{min}) is specific bound counts, % I_{max} is the maximum percent inhibition, % I_{min} is the minimum percent inhibition, radiolabel is the probe, and the K_d is the apparent dissociation constant for the radioligand for the receptor as determined by Hot saturation experiments.

RECOMBINANT RECEPTOR FUNCTIONAL ASSAY: Cells were plated in complete growth medium at 85,000 cells/well in 96-well poly-D-lysine coated plates (Corning) and cultured for ~19 h before assay. Cells were washed with PBS and then incubated with inhibitor for 30 min at 37° C. and 95% humidity in Cellgro Complete Serum-Free/Low-

Protein medium (Mediatech, Inc.) with L-glutamine and 1 g/L BSA. Isobutyl-methylxanthine was added to the cells at a concentration of 300 µM and incubated for 30 min at 37° C. Human α-CGRP was added to the cells at a concentration of 0.3 nM and allowed to incubate at 37° C. for 5 min. After α-CGRP stimulation the cells were washed with PBS and processed for cAMP determination utilizing the two-stage assay procedure according to the manufacturer's recommended protocol (cAMP SPA direct screening assay system; RPA 559; GE Healthcare). Dose response curves were plotted and IC₅₀ values determined from a 4-parameter logistic fit as defined by the equation $y = ((a-d)/(1+(x/c)^b) + d)$, where y=response, x=dose, a=max response, d=min response, c=inflection point and b=slope.

In suitable assays, such as those described herein, the compounds of the invention are expected to have activity as antagonists of the CGRP receptor, generally with a K_i or IC₅₀ value of less than about 50 µM. Such a result is indicative of the intrinsic activity of the compounds of the invention as antagonists of CGRP receptors.

Exemplary K_i values in the recombinant receptor binding assay for exemplary compounds of the invention are provided in the table below:

Example	K _i (nM)
1	25
2	570
3	2600
4	6400
6	630
7	35
8	130
9	160
11	0.21
12	29
13	1.6

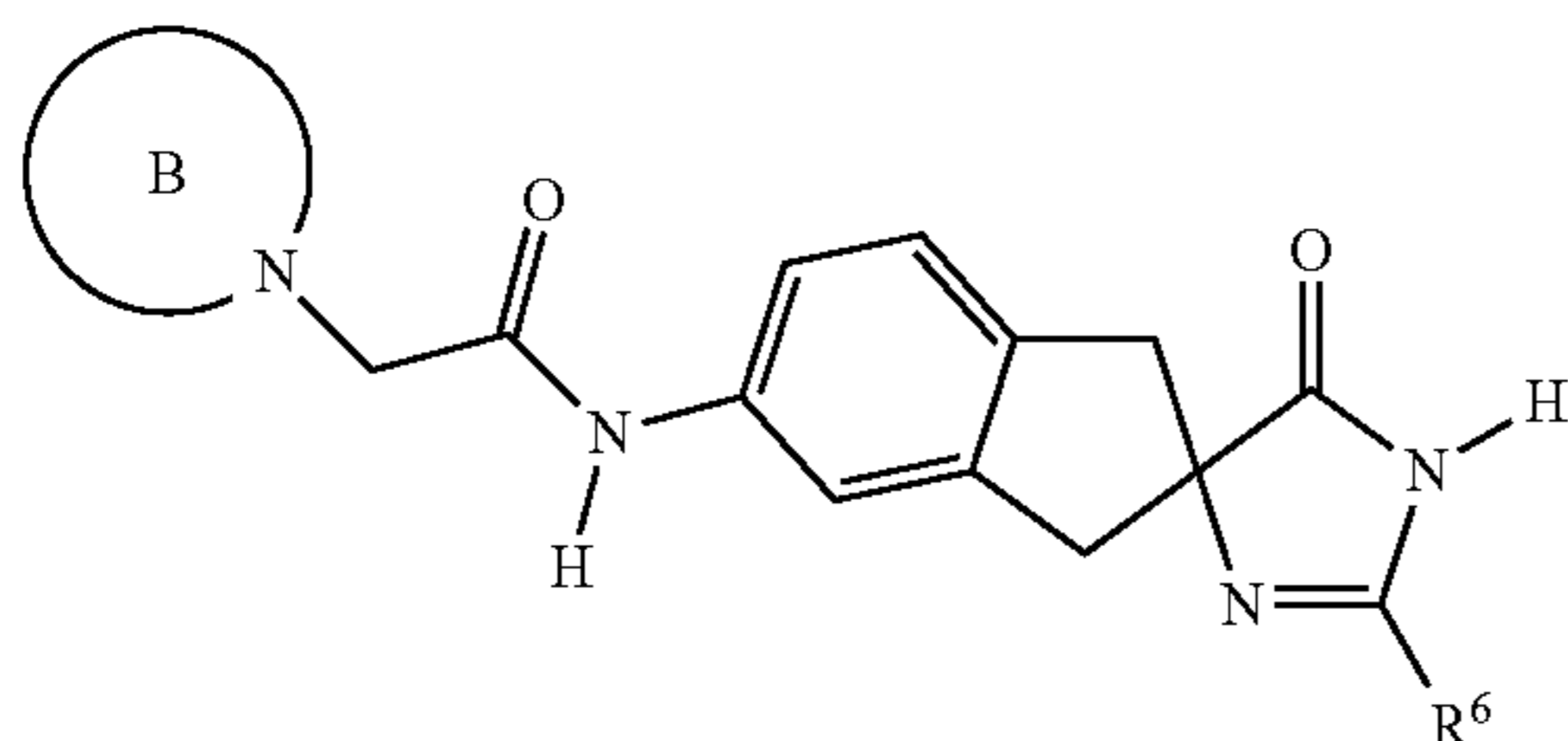
While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth

herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

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What is claimed is:

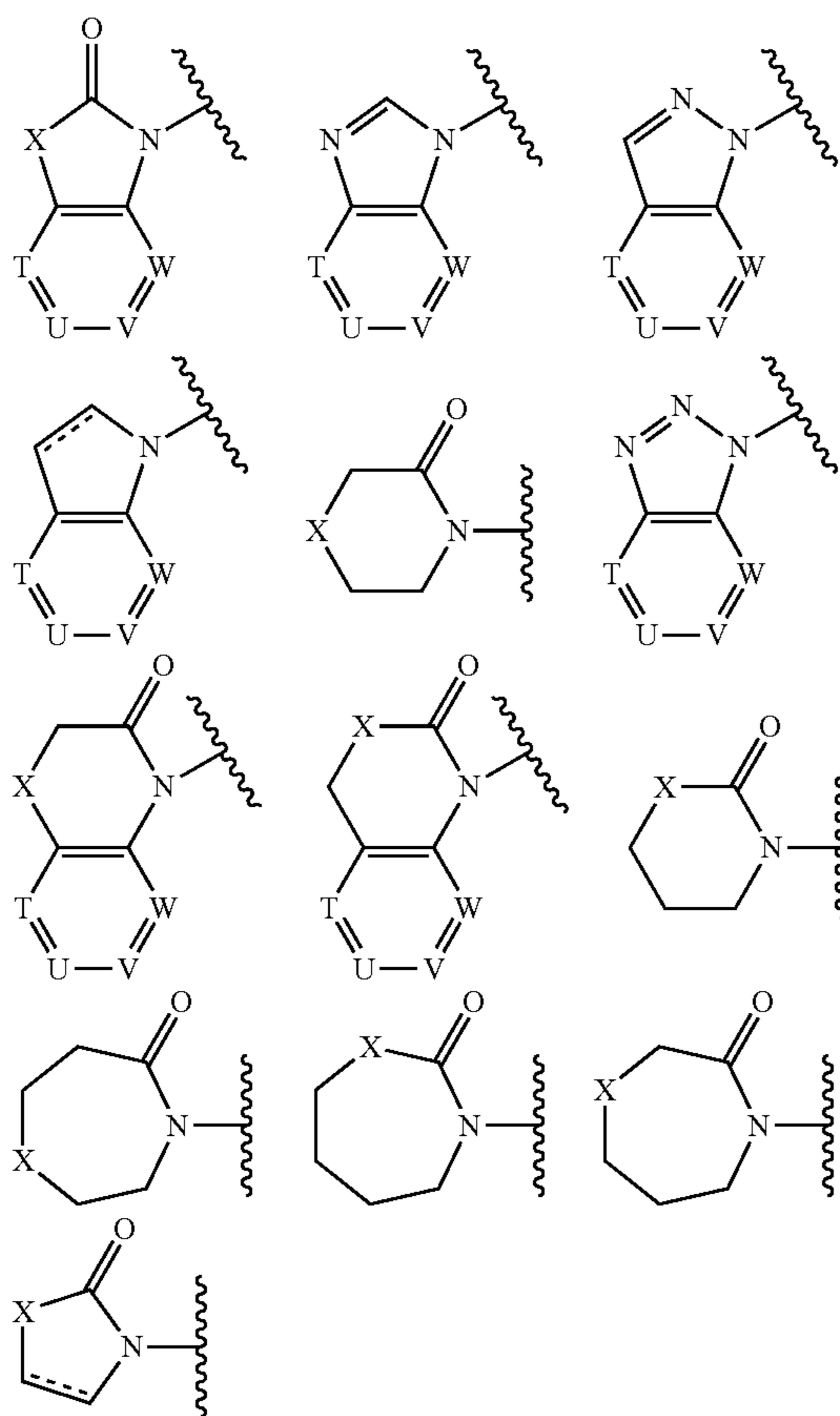
1. A compound of formula ID:



ID 5

wherein:

B is a heterocycle selected from the group consisting of:



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wherein T, U, V, and W are each independently a carbon atom or a nitrogen atom, wherein no more than two of T, U, V and W are nitrogen atoms;

wherein X is selected from:

- (1) —O—,
- (2) —S(O)_q—,
- (3) —Si(OR^a)—C₁₋₄alkyl-, where alkyl is unsubstituted or substituted with 1-5 halo,
- (4) —Si(C₁₋₄alkyl)₂-, where each alkyl is independently unsubstituted or substituted with 1-5 halo-,
- (5) —N(R⁸)—,
- (6) —(C=O)—,
- (7) —C(R⁸)(R^a)—,
- (8) —C(N(R^b))—SO₂R^d(R^a)—,

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- (9) —C(N(R^b))(C=O)R^a(R^a)—,
- (10) —C(N(R^b))(C=O)OR^a(R^a)—,
- (11) —CR¹⁰R¹¹—,
- (12) —N(R¹¹)—, and
- (13) —CR³R⁴—;

B is unsubstituted or substituted with 1-7 substituents each independently selected from R¹, R², R³, R⁴, R¹⁰, and R¹¹, wherein R¹, R², and R³ are independently selected from:

- (1) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 - (a) halo,
 - (b) hydroxy,
 - (c) —O—C₁₋₆alkyl,
 - (d) —C₃₋₆cycloalkyl,
 - (e) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, oxazolyl, thiazolyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from: —C₁₋₆alkyl, —O—C₁₋₆alkyl, halo, hydroxy, trifluoromethyl and —OCF₃,
 - (f) —CO₂R¹⁹,
 - (g) —NR²⁰R²¹,
 - (h) —SO₂R²²,
 - (i) —CONR^{20a}R^{21a},
 - (j) trifluoromethyl,
 - (k) —OCO₂R¹⁹,
 - (l) —(NR^{20a})CO₂R¹⁹,
 - (m) —O(CO)NR^{20a}R^{21a},
 - (n) —(NR¹⁹)(CO)NR^{20a}R^{21a}, and
 - (o) —O—C₃₋₆cycloalkyl,
- (2) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 - (a) halo,
 - (b) hydroxy,
 - (c) —O—C₁₋₆alkyl,
 - (d) trifluoromethyl,
 - (e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: —C₁₋₆alkyl, —O—C₁₋₆alkyl, halo, hydroxy and trifluoromethyl,
- (3) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, thienyl, pyridazinyl, pyrrolidinyl, azetidyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, azepanyl, benzimidazolyl, benzopyranyl, benzofuryl, benzothiazolyl, benzoxazolyl, chromanyl, furyl, imidazolyl, indolyl, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, isoindolyl, tetrahydroisoquinolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, pyrazolidinyl, pyrazolyl, pyrrolyl, quinazolyl, tetrahydrofuryl, thiazolyl, purinyl, naphthyridinyl, quinoxalyl, 1,3-dioxolanyl, oxadiazolyl, piperidinyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiopyranyl, and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
 - (b) halo,
 - (c) hydroxy,

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- (d) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
- (e) —C₃₋₆cycloalkyl,
- (f) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, thienyl, or morpholinyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from: —C₁₋₆alkyl, —O—C₁₋₆alkyl, halo, hydroxy and trifluoromethyl,
- (g) —CO₂R¹⁹,
- (h) —(CO)R¹⁹,
- (i) —NR²⁰R²¹,
- (j) —CONR²⁰R²¹,
- (k) oxo, and
- (l) —S(O)_qR²²,
- (4) halo,
- (5) oxo,
- (6) hydroxy,
- (7) —O—C₁₋₆alkyl which is unsubstituted or substituted with 1-5 halo,
- (8) —CN,
- (9) —CO₂R¹⁹,
- (10) —NR²⁰R²¹,
- (11) —SO₂R²²,
- (12) —CONR^{20a}R^{21a},
- (13) —OCO₂R¹⁹,
- (14) —(NR^{20a})CO₂R¹⁹,
- (15) —O(CO)NR^{20a}R^{21a},
- (16) —(NR¹⁹)(CO)NR^{20a}R^{21a},
- (17) —(CO)—(CO)NR^{20a}R^{21a},
- (18) —(CO)—(CO)OR¹⁹,
- (19) —SO₂NR^{20a}R^{21a}, and
- (20) hydrogen;
- or R³ and R⁴ and the carbon atom to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, dioxolanyl, dioxanyl, aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiapyranyl, oxetanyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from:
- (i) halo,
- (ii) —OR^a,
- (iii) —C₃₋₆cycloalkyl,
- (iv) —CO₂R^a,
- (v) —NR^bR^c,
- (vi) —S(O)_qR^d,
- (vii) —C(=O)NR^bR^c, and
- (viii) phenyl,
- (b) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, wherein the phenyl or heterocycle is optionally fused to the ring, and which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (i) halo,
- (ii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,

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- (iii) —OR^a,
- (iv) —CO₂R^a,
- (v) —O(C=O)R^a,
- (vi) —CN,
- (vii) —NR^bR^c,
- (viii) oxo,
- (ix) —C(=O)NR^bR^c,
- (x) —N(R^b)C(=O)R^a,
- (xi) —N(R^b)CO₂R^a,
- (xii) —O(C=O)NR^bR^c, and
- (xiii) —S(O)_qR^d,
- (c) —OR^a,
- (d) halo,
- (a) —CO₂R^a,
- (b) —C(=O)NR^bR^c,
- (c) —S(O)_qR^d,
- (d) —CN,
- (e) —NR^bR^c,
- (f) —N(R^b)C(=O)R^a,
- (g) —N(R^b)SO₂R^d,
- (h) —O—CO₂R^d,
- (i) —O—(C=O)—NR^bR^c,
- (j) —NR^b—(C=O)—NR^bR^c,
- (k) —C(=O)R^a, and
- (l) oxo;
- R⁴ is independently selected from:
- (1) hydrogen,
- (2) —C(=O)R^a,
- (3) —CO₂R^a,
- (4) —S(=O)R^d,
- (5) —SO₂R^d,
- (6) —C(=O)NR^bR^c,
- (7) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (a) halo,
- (b) —OR^a,
- (c) —C₃₋₆cycloalkyl,
- (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (i) halo,
- (ii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
- (iii) —OR^a,
- (iv) —NR^bR^c,
- (v) —C(=O)R^a,
- (vi) —CO₂R^a, and
- (vii) oxo;
- (e) —CO₂R^a,
- (f) —C(=O)NR^bR^c,
- (g) —S(O)_qR^d,
- (h) —CN,
- (i) —NR^bR^c,
- (j) —N(R^b)C(=O)R^a,
- (k) —N(R^b)SO₂R^d,
- (l) —CF₃,
- (m) —O—CO₂R^d,
- (n) —O—(C=O)—NR^bR^c,
- (o) —NR^b—(C=O)—NR^bR^c, and
- (p) —C(=O)R^a;

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- (c) —C₃₋₆cycloalkyl,
 (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, 5 which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (i) halo,
 (ii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo, 10
 (iii) —OR^a,
 (iv) —NR^bR^c,
 (v) —C(=O)R^a,
 (vi) —CO₂R^a, 15
 (vii) oxo, and
 (viii) —CN,
 (e) —CO₂R^a,
 (f) —C(=O)NR^bR^c,
 (g) —S(O)_qR^d, 20
 (h) —CN,
 (i) —NR^bR^c,
 (j) —N(R^b)C(=O)R^a,
 (k) —N(R^b)SO₂R^d,
 (l) —CF₃, 25
 (m) —O—CO₂R^d,
 (n) —O—C(=O)—NR^bR^c,
 (o) —NR^b—C(=O)—NR^bR^c, and
 (p) —C(=O)R^a,
 (8) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from: 30
 (a) halo,
 (b) —CN,
 (c) —OR^a, and 35
 (d) C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo;
 or R⁴ and R⁸ and the atoms to which they are attached join to form a 4-, 5-, 6- or 7-membered alkyl- or heteroalkyl-ring optionally containing an additional heteroatom 40 selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:
- (a) halo, 45
 (b) phenyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: halo, OR^a, CN, and —C(=O)OR^a,
 (c) —OR^a, and
 (d) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halo; 50
 R¹⁰ is selected from:
- (1) hydrogen,
 (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: 55
 (a) halo,
 (b) —OR^a,
 (c) —CN,
 (d) phenyl, and 60
 (e) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 (3) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo;
 R¹¹ is selected from the group consisting of: 65
 phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl, azepinyl, azepanyl, azetid-

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- nyl, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, chromanyl, cinnolinyl, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, furanyl, imidazolidiny, imidazoliny, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, morpholinyl, naphthyridinyl, oxazolyl, oxadiazolyl, 2-oxoazepinyl, 4-oxonaphthyridinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxopyridyl, 2-oxoquinolinyl, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, quinazoliny, quinolinyl, quinoxaliny, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, thiazolyl, thiazolinyl, thienofuryl, thienothiényl, thienyl, triazolyl, isoxazolyl, tetrahydrothienyl, tetrahydropyranyl, oxetanyl, tetrahydrothiapyranyl, and thietanyl, where R¹¹ is unsubstituted or substituted with 1-5 substituents each independently selected from R¹², R¹³, R¹⁴, R^{15a} and R^{15b};
 R¹², R¹³, R¹⁴, R^{15a} and R^{15b} are each independently selected from:
 (1) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) halo,
 (b) —OR^a,
 (c) —C₃₋₆cycloalkyl,
 (d) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (i) halo,
 (ii) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo, and
 (iii) —OR^a,
 (e) —CO₂R^a,
 (f) —C(=O)NR^bR^c,
 (g) —S(O)_qR^d,
 (h) —CN,
 (i) —NR^bR^c,
 (j) —N(R^b)C(=O)R^a,
 (k) —N(R^b)SO₂R^d,
 (l) —CF₃,
 (m) —O—CO₂R^d,
 (n) —O—C(=O)—NR^bR^c,
 (o) —NR^b—C(=O)—NR^bR^c, and
 (p) —C(=O)R^a,
 (2) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 (a) halo,
 (b) —CN,
 (c) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 (d) —OR^a, and

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- (e) phenyl, which is unsubstituted or substituted with 1-5 substituents where the substituents are each independently selected from:
- (i) $-\text{OR}^a$,
 - (ii) halo, 5
 - (iii) $-\text{CN}$, and
 - (iv) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
- (3) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from: 15
- (a) halo,
 - (b) $-\text{OR}^a$,
 - (c) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 - (d) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: 20
 - (i) halo,
 - (ii) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo, and
 - (iii) $-\text{OR}^a$, 25
 - (e) $-\text{CO}_2\text{R}^a$,
 - (f) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$,
 - (g) $-\text{S}(\text{O})_q\text{R}^d$,
 - (h) $-\text{CN}$,
 - (i) $-\text{NR}^b\text{R}^c$, 30
 - (j) $-\text{N}(\text{R}^b)\text{C}(=\text{O})\text{R}^a$,
 - (k) $-\text{N}(\text{R}^b)\text{SO}_2\text{R}^d$,
 - (l) $-\text{O}-\text{CO}_2\text{R}^d$,
 - (m) $-\text{O}-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$,
 - (n) $-\text{NR}^b-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$, 35
 - (o) $-\text{C}(=\text{O})\text{R}^a$, and
 - (p) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
- (4) halo,
- (5) oxo, 40
- (6) $-\text{OR}^a$,
 - (7) $-\text{CN}$,
 - (8) $-\text{CO}_2\text{R}^a$,
 - (9) $-\text{C}(=\text{O})\text{R}^a$,
 - (10) $-\text{NR}^b\text{R}^c$, 45
 - (11) $-\text{S}(\text{O})_q\text{R}^d$,
 - (12) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$,
 - (13) $-\text{O}-\text{CO}_2\text{R}^d$,
 - (14) $-\text{N}(\text{R}^b)\text{CO}_2\text{R}^d$,
 - (15) $-\text{O}-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$, 50
 - (16) $-\text{NR}^b-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$,
 - (17) $-\text{SO}_2\text{NR}^b\text{R}^c$,
 - (18) $-\text{N}(\text{R}^b)\text{SO}_2\text{R}^d$,
- or R^{15a} and R^{15b} and the atom(s) to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from: 60
- (a) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-3 substituents each independently selected from: 65
 - (i) halo,
 - (ii) $-\text{OR}^a$,

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- (iii) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 - (iv) $-\text{CO}_2\text{R}^a$,
 - (v) $-\text{NR}^b\text{R}^c$,
 - (vi) $-\text{S}(\text{O})_q\text{R}^d$,
 - (vii) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$, and
 - (viii) phenyl,
- (b) phenyl or heterocycle, wherein said heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
- (i) halo,
 - (ii) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo, and
 - (iii) $-\text{OR}^a$,
- (c) $-\text{OR}^a$,
- (d) halo,
- (e) $-\text{CO}_2\text{R}^a$,
- (f) $-\text{C}(=\text{O})\text{NR}^b\text{R}^c$,
- (g) $-\text{S}(\text{O})_q\text{R}^d$,
- (h) $-\text{CN}$,
- (i) $-\text{NR}^b\text{R}^c$,
- (j) $-\text{N}(\text{R}^b)\text{C}(=\text{O})\text{R}^a$,
- (k) $-\text{N}(\text{R}^b)\text{SO}_2\text{R}^d$,
- (l) $-\text{O}-\text{CO}_2\text{R}^d$,
- (m) $-\text{O}-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$,
- (n) $-\text{NR}^b-\text{C}(=\text{O})-\text{NR}^b\text{R}^c$, and
- (o) $-\text{C}(=\text{O})\text{R}^a$;
- R^{19} is selected from:
- (1) hydrogen,
 - (2) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 substituents, each independently selected from:
 - (a) halo,
 - (b) hydroxy,
 - (c) $-\text{OC}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (d) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo, and
 - (e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (i) $-\text{C}_{1-4}$ alkyl,
 - (ii) $-\text{OC}_{1-6}$ alkyl,
 - (iii) halo,
 - (iv) trifluoromethyl, and
 - (v) $-\text{OCF}_3$,
- (3) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 substituents, substituents each independently selected from:
- (a) halo,
 - (b) hydroxy,
 - (c) $-\text{O}-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (d) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with 1-5 halo, and
 - (e) phenyl,
- (4) phenyl or heterocycle, wherein heterocycle is selected from: pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, pyrrolidinyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, imidazoliny, indoliny, indolyl, quinoliny, isoquinoliny, tetrahydroquinoliny, isoindoliny, tetrahydroisoquinoliny, tetrahydrofuryl, quinoxaliny, piperidinyl, piperazinyl, and

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morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (a) halo,
- (b) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo 5
- (c) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo
- (d) —C₃₋₆cycloalkyl,
- (e) oxo, 10
- (f) —CN,
- (g) hydroxy, and
- (h) phenyl;

R²⁰ and R²¹ are each independently selected from:

- (1) hydrogen, 15
- (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from:
 - (a) halo,
 - (b) hydroxy, 20
 - (c) —OCF₃,
 - (d) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo, and
 - (e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: 25
 - (i) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (ii) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (iii) —CN, 30
 - (iv) halo, and
 - (v) trifluoromethyl,
- (3) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
- (4) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: 35
 - (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo, 40
 - (c) halo,
 - (d) hydroxy,
 - (e) trifluoromethyl,
 - (f) —OCF₃, and
 - (g) —CN, 45
- (5) —COR¹⁹, and
- (6) —SO₂R²²;

R^{20a} and R^{21a} are each independently selected from:

- (1) hydrogen,
- (2) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 substituents each independently selected from: 50
 - (a) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) halo, 55
 - (c) hydroxy,
 - (d) —OCF₃,
 - (e) —C₃₋₆cycloalkyl, and
 - (f) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: 60
 - (i) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (ii) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (iii) —CN 65
 - (iv) halo, and
 - (v) trifluoromethyl,

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(3) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-5 halo,

(4) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
- (b) —OC₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
- (c) halo,
- (d) hydroxy,
- (e) trifluoromethyl,
- (f) —OCF₃, and
- (g) —CN,

or where R^{20a} and R^{21a} join to form a ring selected from azetidiny, pyrrolidinyl, piperidinyl, azepanyl, piperazinyl and morpholinyl, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (1) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
- (2) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
- (3) halo,
- (4) hydroxy,
- (5) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo,
 - (b) —O—C₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo, and
 - (c) halo,
- (6) benzyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo,
 - (b) —OC₁₋₄alkyl, which is unsubstituted or substituted with 1-3 halo, and
 - (c) halo,
- (7) —COR¹⁹, and
- (8) —SO₂R²²;

R²² is selected from:

- (1) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
- (2) —C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-5 halo,
- (3) phenyl or heterocycle, wherein heterocycle is selected from: pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (a) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (b) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (c) halo,
 - (d) hydroxy,
 - (e) trifluoromethyl,
 - (f) —OCF₃,
 - (g) —CN, and
 - (h) benzyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from:
 - (i) —C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,
 - (ii) —O—C₁₋₆alkyl, which is unsubstituted or substituted with 1-5 halo,

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- (iii) halo, and
- (iv) trifluoromethyl;

R^a is independently selected from:

- (1) hydrogen,
- (2) C_{1-6} alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 - (a) halo,
 - (b) $-O-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
 - (c) hydroxyl,
 - (d) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
 - (e) $-CN$, and
 - (f) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuran, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
 - (i) halo,
 - (ii) $-O-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
 - (iii) $-CN$,
 - (iv) nitro,
 - (v) hydroxyl, and
 - (vi) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,

- (3) phenyl or heterocycle wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl morpholinyl, tetrahydrofuran, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
 - (a) halo,
 - (b) $-CN$,
 - (c) $-O-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
 - (d) nitro,
 - (e) hydroxyl, and
 - (f) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo, and

- (4) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

R^b and R^c are independently selected from:

- (1) hydrogen,
- (2) C_{1-6} alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 - (a) halo,
 - (b) $-OR^a$,
 - (c) $-CN$,
 - (d) $-CO_2R^a$,
 - (e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuran, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
 - (i) halo,
 - (ii) $-OR^a$,
 - (iii) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo, and
 - (iv) nitro,
- (3) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazi-

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nyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuran, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

- (a) halo,
- (b) $-OR^a$,
- (c) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
- (d) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
- (e) $-CN$, and
- (f) $-CO_2R^a$,
- (4) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

or R^b and R^c and the nitrogen to which they are attached join to form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N, O, and S, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-4 substituents each independently selected from:

- (i) halo,
- (ii) $-OR^a$, and
- (iii) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo, and
- (iv) phenyl;

R^d is independently selected from:

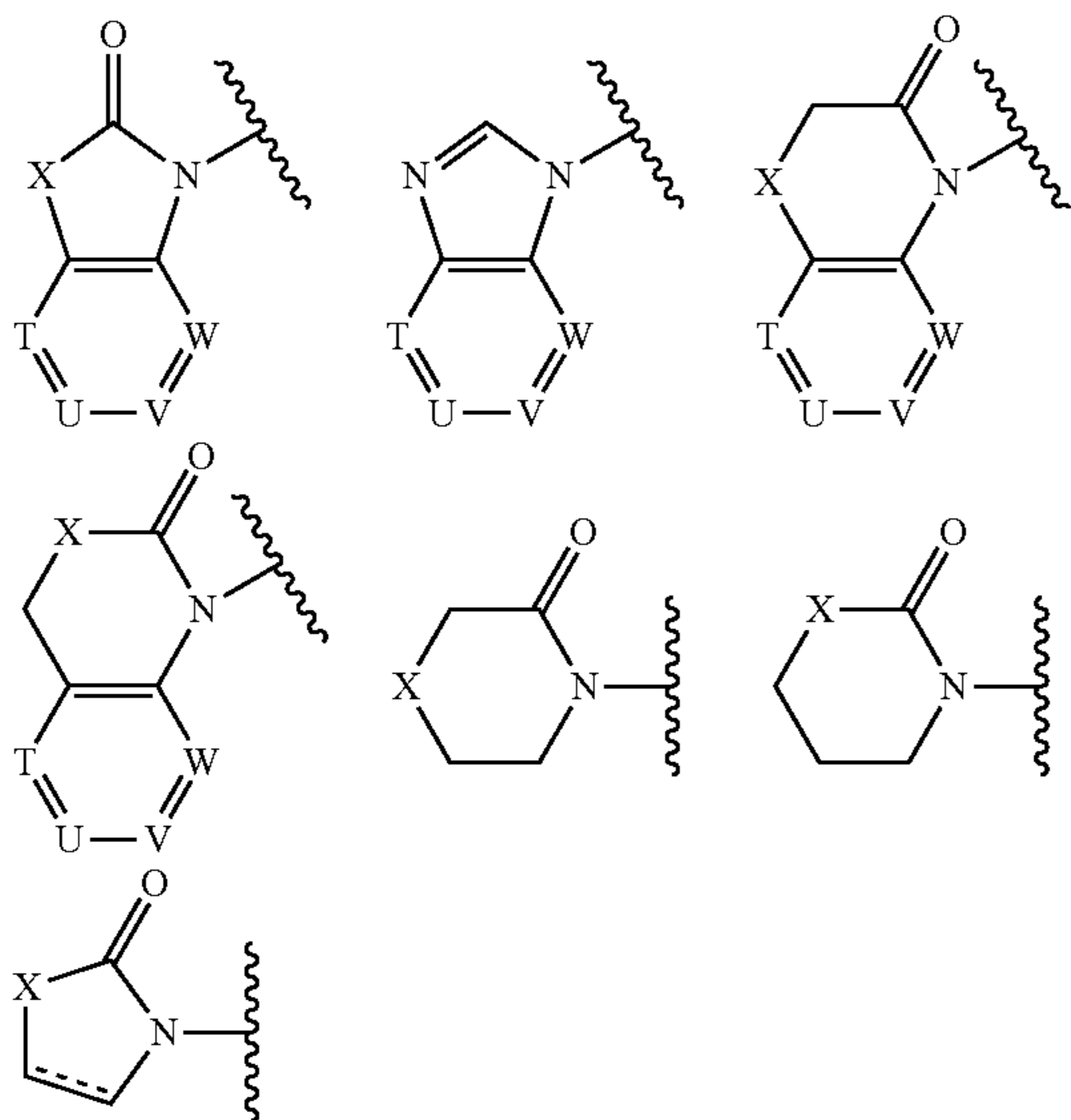
- (1) C_{1-6} alkyl, which is unsubstituted or substituted with 1-4 substituents each independently selected from:
 - (a) halo,
 - (b) $-OR^a$,
 - (c) $-CO_2R^a$,
 - (d) $-CN$, and
 - (e) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuran, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:
 - (i) halo,
 - (ii) $-OR^a$,
 - (iii) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo, and
 - (iv) nitro,
- (2) phenyl or heterocycle, wherein said heterocycle is selected from pyridyl, pyrimidinyl, thienyl, pyridazinyl, piperidinyl, azetidiny, furanyl, piperazinyl, pyrrolidinyl, morpholinyl, tetrahydrofuran, tetrahydropyranyl and pyrazinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-3 substituents each independently selected from:

- (a) halo,
- (b) $-OR^a$,
- (c) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halo,
- (d) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo,
- (e) $-CN$, and
- (f) $-CO_2R^a$, and
- (3) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-6 halo;

q is 0, 1, or 2;
or a pharmaceutically acceptable salt thereof and individual enantiomers and diastereomers thereof.

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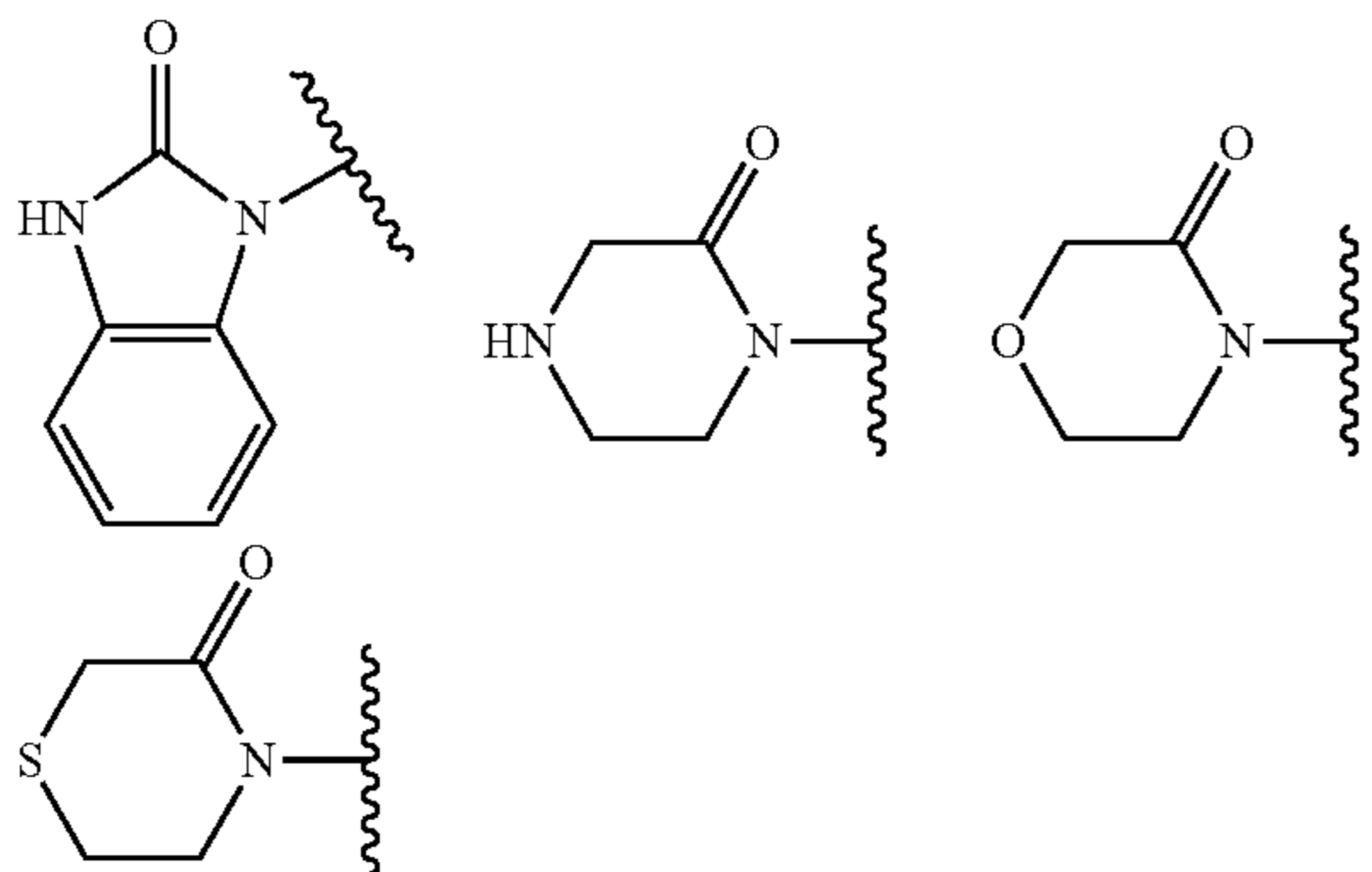
2. A compound of claim 1 wherein B is selected from the group consisting of:



which is unsubstituted or substituted with 1-7 substituents each independently selected from R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} , wherein T, U, V, W, X, R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} are defined herein;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

3. A compound of claim 2, wherein B is selected from the group consisting of:



which is unsubstituted or substituted with 1-7 substituents each independently selected from R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} , wherein R^1 , R^2 , R^3 , R^4 , R^{10} , and R^{11} are defined herein;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

4. A compound of any of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , and R^3 are each independently selected from:

- (1) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:
 - (a) fluoro,
 - (b) hydroxy,
 - (c) $-O-C_{1-6}$ alkyl,
 - (d) $-C_{3-6}$ cycloalkyl,
 - (e) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl,

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pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, oxazolyl, thiazolyl, thienyl and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from: $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, halo, hydroxy, trifluoromethyl and $-OCF_3$,

- (f) $-CO_2R^{19}$
- (g) $-NR^{20}R^{21}$,
- (h) $-SO_2R^{22}$,
- (i) $-CONR^{20a}R^{21a}$,
- (j) trifluoromethyl,
- (k) $-(NR^{20a})CO_2R^{19}$,
- (l) $-(NR^{19})(CO)NR^{20a}R^{21a}$, and
- (m) $-O-C_{3-6}$ cycloalkyl,

(2) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with 1-7 substituents each independently selected from:

- (a) fluoro,
- (b) hydroxy,
- (c) $-O-C_{1-6}$ alkyl,
- (d) trifluoromethyl, and
- (e) phenyl, which is unsubstituted or substituted with 1-5 substituents each independently selected from: $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, halo, hydroxy and trifluoromethyl,

(3) phenyl or heterocycle, wherein heterocycle is selected from:

pyridyl, pyrimidinyl, pyrazinyl, thienyl, pyridazinyl, pyrrolidinyl, azetidiny, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, azepanyl, benzimidazolyl, benzopyranyl, benzofuryl, benzothiazolyl, benzoxazolyl, chromanyl, furyl, imidazoliny, indoliny, indolyl, quinoliny, isoquinoliny, tetrahydroquinoliny, isoindoliny, tetrahydroisoquinoliny, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, pyrazolidinyl, pyrazolyl, pyrrolyl, quinazoliny, tetrahydrofuryl, thiazoliny, puriny, naphthyridiny, quinoxaliny, 1,3-dioxolany, oxadiazolyl, piperidinyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiopyranyl, and morpholinyl, which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (a) $-CF_3$,
- (b) halo,
- (c) hydroxy,
- (d) $-O-CF_3$,
- (e) $-C_{3-6}$ cycloalkyl,
- (f) $-CO_2R^{19}$,
- (g) $-(CO)R^{19}$,
- (h) $-CONR^{20}R^{21}$,
- (i) oxo, and
- (j) $-S(O)_qR^{22}$,

(4) halo,

(5) oxo,

(6) hydroxy,

(7) $-O-C_{1-6}$ alkyl which is unsubstituted or substituted with 1-5 halo,

(8) $-CN$,

(9) $-CO_2R^{19}$,

(10) $-NR^{20}R^{21}$,

(11) $-SO_2R^{22}$,

(12) $-CONR^{20a}R^{21a}$,

(13) $-SO_2NR^{20a}R^{21a}$, and

(14) hydrogen.

5. A compound of any of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 and the carbon atom to which they are attached join to form a ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, dioxolany, dioxanyl, aziridinyl, azetidiny, pyr-

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rolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiapyranyl, oxetanyl, thietanyl and tetrahydrothienyl, wherein the sulfur is optionally oxidized to the sulfone or sulfoxide, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from:

(a) $\text{—C}_{1-6}\text{alkyl}$, which is unsubstituted or substituted with 1-3 substituents each independently selected from:

- (i) halo,
- (ii) —OR^a ,
- (iii) $\text{—C}_{3-6}\text{cycloalkyl}$,
- (iv) $\text{—CO}_2\text{R}^a$,
- (v) $\text{—NR}^b\text{R}^c$,
- (vi) $\text{—S(O)}_q\text{R}^d$,
- (vii) $\text{—C(=O)NR}^b\text{R}^c$, and
- (viii) phenyl,

(b) phenyl or heterocycle, wherein heterocycle is selected from: pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, morpholinyl, thiazolyl and oxazolyl, wherein the phenyl or heterocycle is optionally fused to the ring, and which phenyl or heterocycle is unsubstituted or substituted with 1-5 substituents each independently selected from:

- (i) halo,
- (ii) —CF_3 ,
- (iii) —OR^a ,
- (iv) $\text{—CO}_2\text{R}^a$,
- (v) —O(C=O)R^a ,
- (vi) —CN ,
- (vii) oxo, and
- (viii) $\text{—C(=O)NR}^b\text{R}^c$,

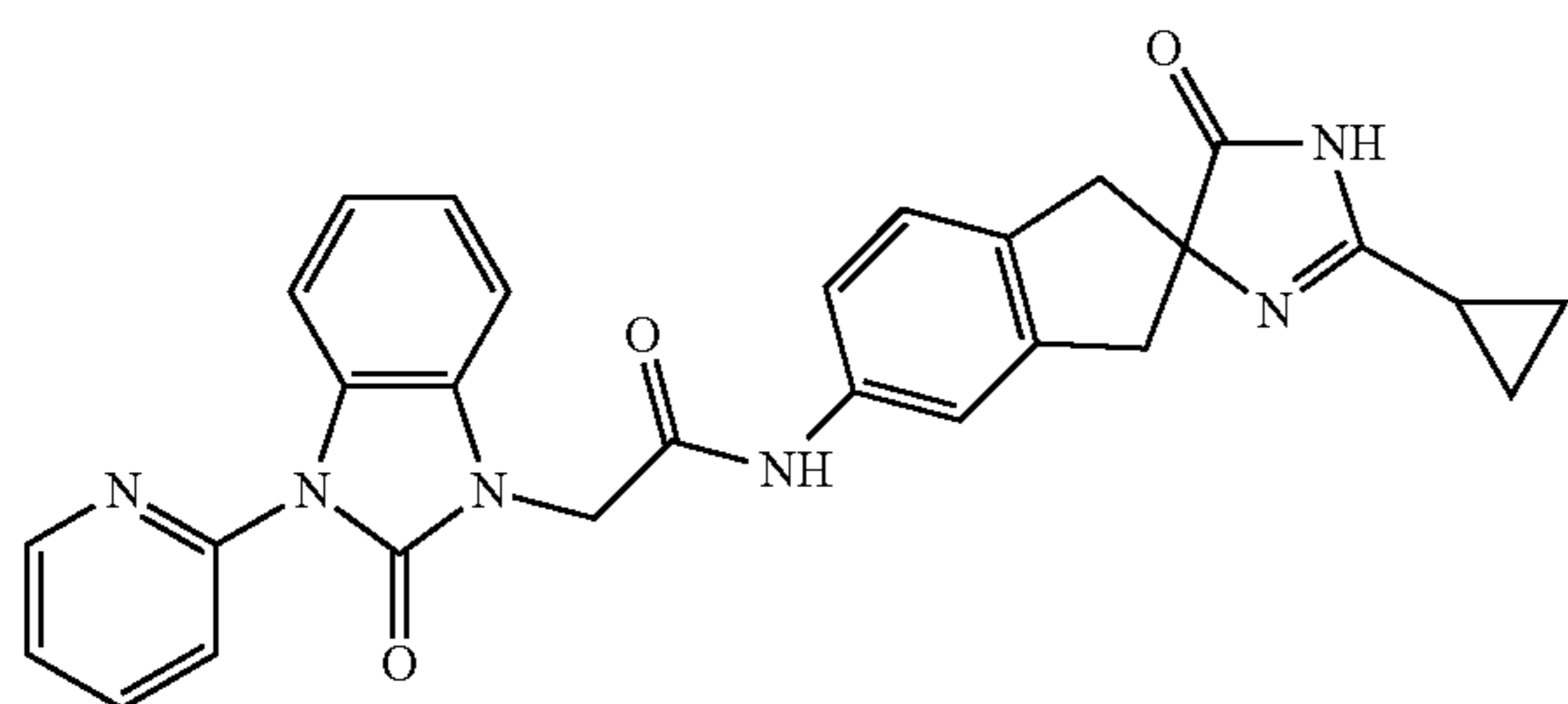
- (c) halo,
- (d) $\text{—CO}_2\text{R}^a$,
- (e) $\text{—C(=O)NR}^b\text{R}^c$,
- (f) —CN ,
- (g) —C(=O)R^a , and
- (h) oxo.

6. A compound of any of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is selected from:

- (1) —O— ,
- (2) $\text{—S(O)}_q\text{—}$,
- (3) $\text{—N(R}^8\text{)—}$,
- (4) —(C=O)— ,
- (5) $\text{—C(R}^8\text{)(R}^a\text{)—}$,
- (6) $\text{—C(N(R}^b\text{)—SO}_2\text{R}^d\text{)(R}^a\text{)—}$,
- (7) $\text{—C(N(R}^b\text{)(C=O)R}^a\text{)(R}^a\text{)—}$,
- (8) $\text{—C(N(R}^b\text{)(C=O)OR}^a\text{)(R}^a\text{)—}$,
- (9) $\text{—CR}^{10}\text{R}^{11}\text{—}$,
- (10) $\text{—N(R}^{11}\text{)—}$, and
- (11) $\text{—CR}^3\text{R}^4\text{—}$.

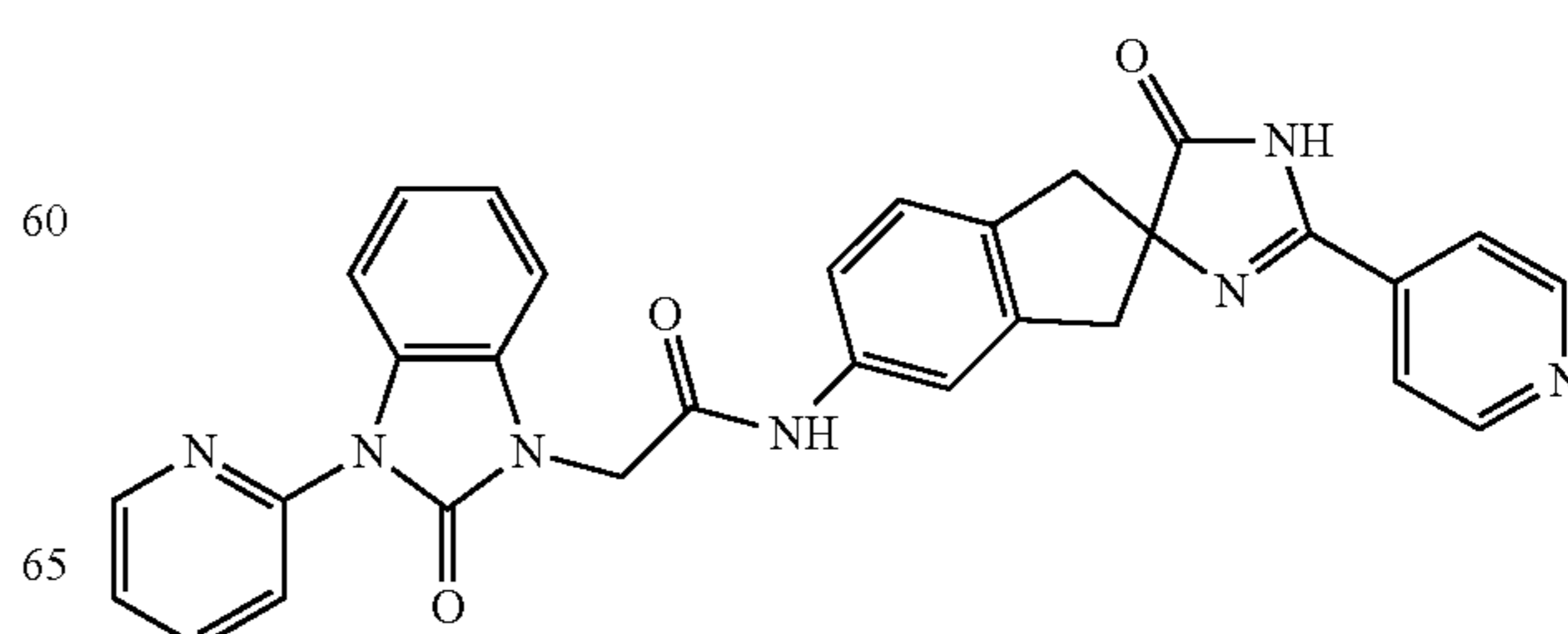
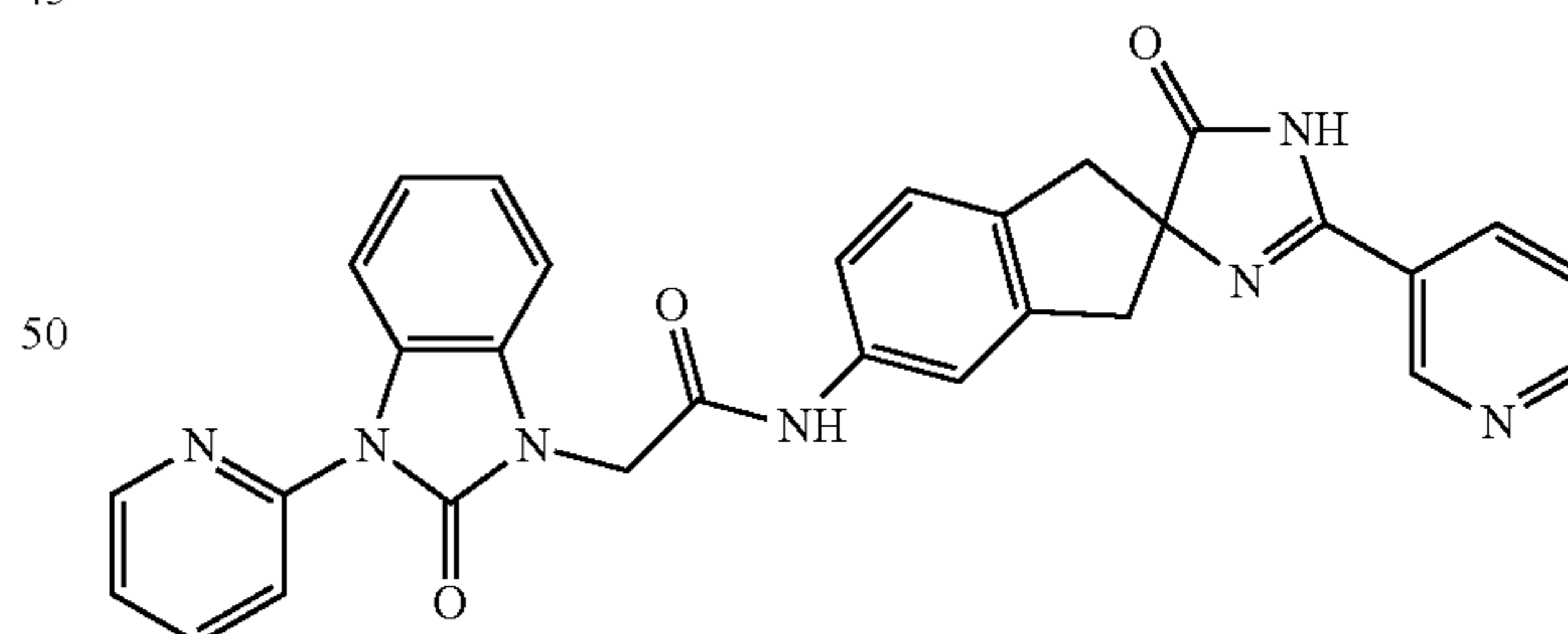
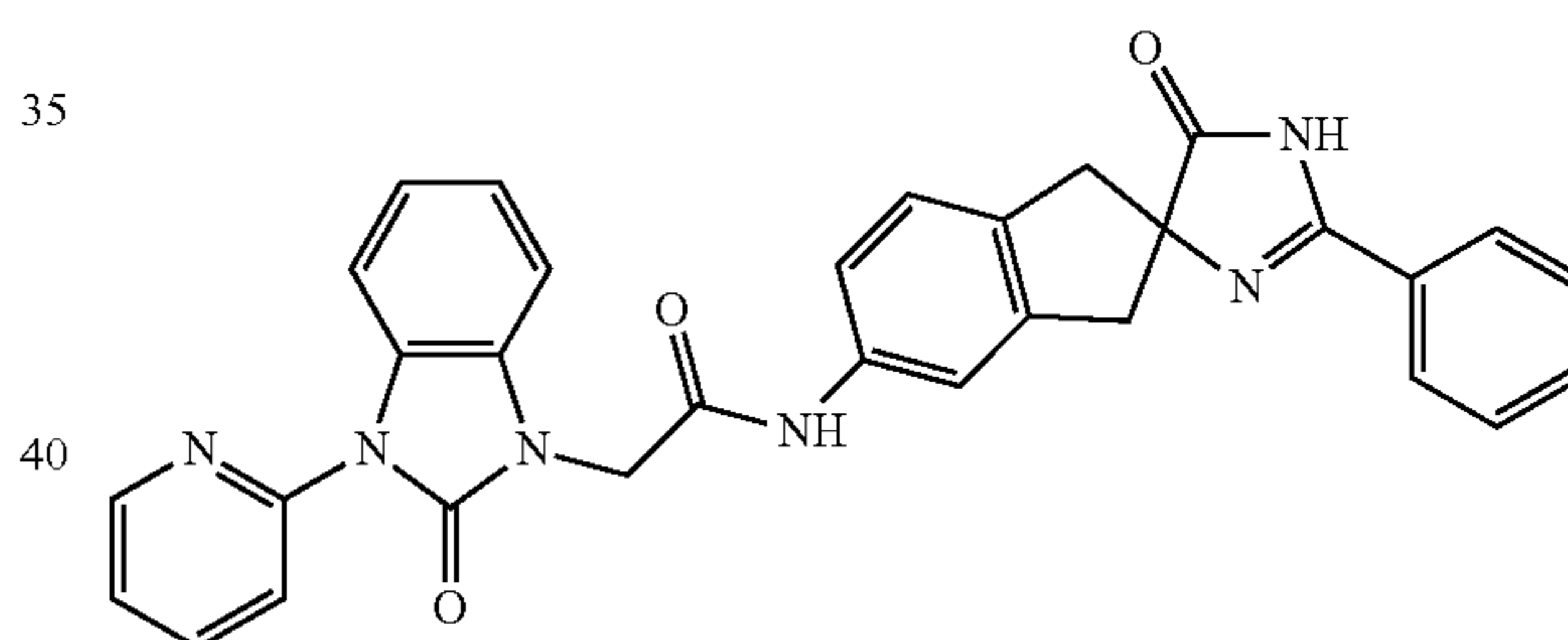
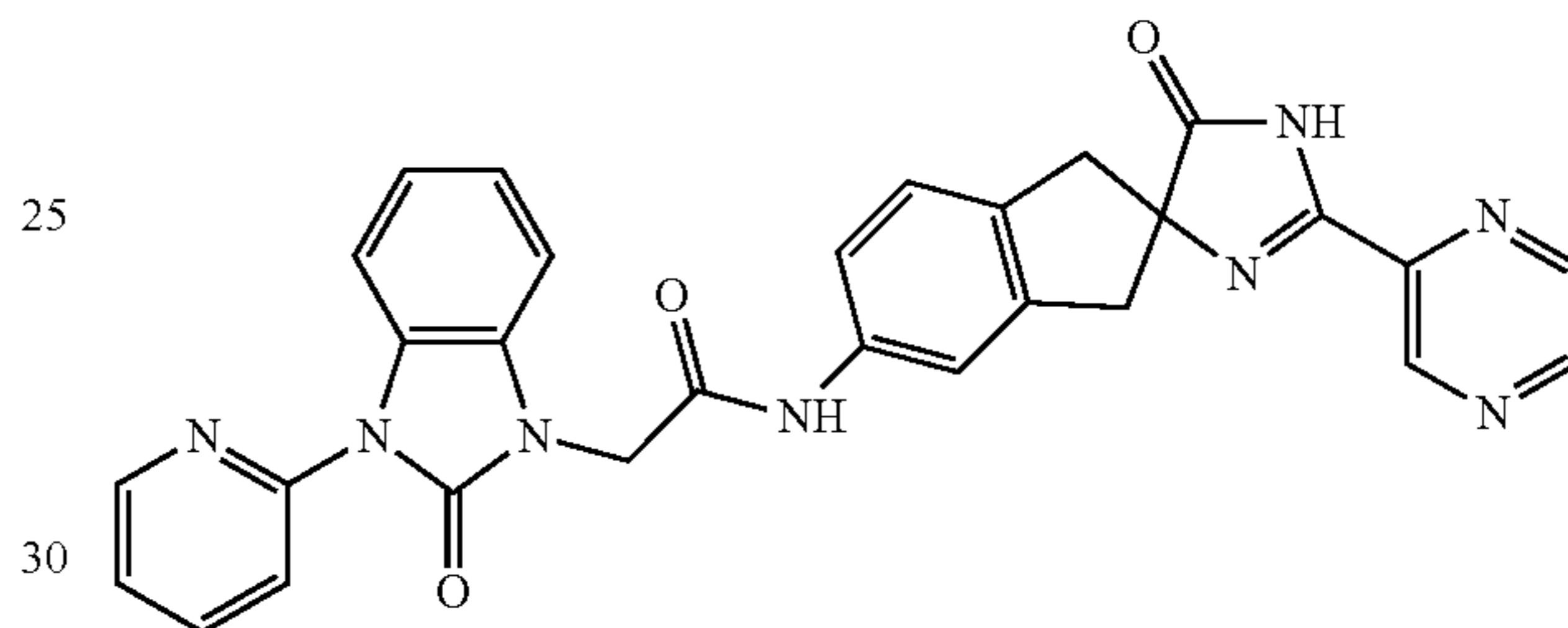
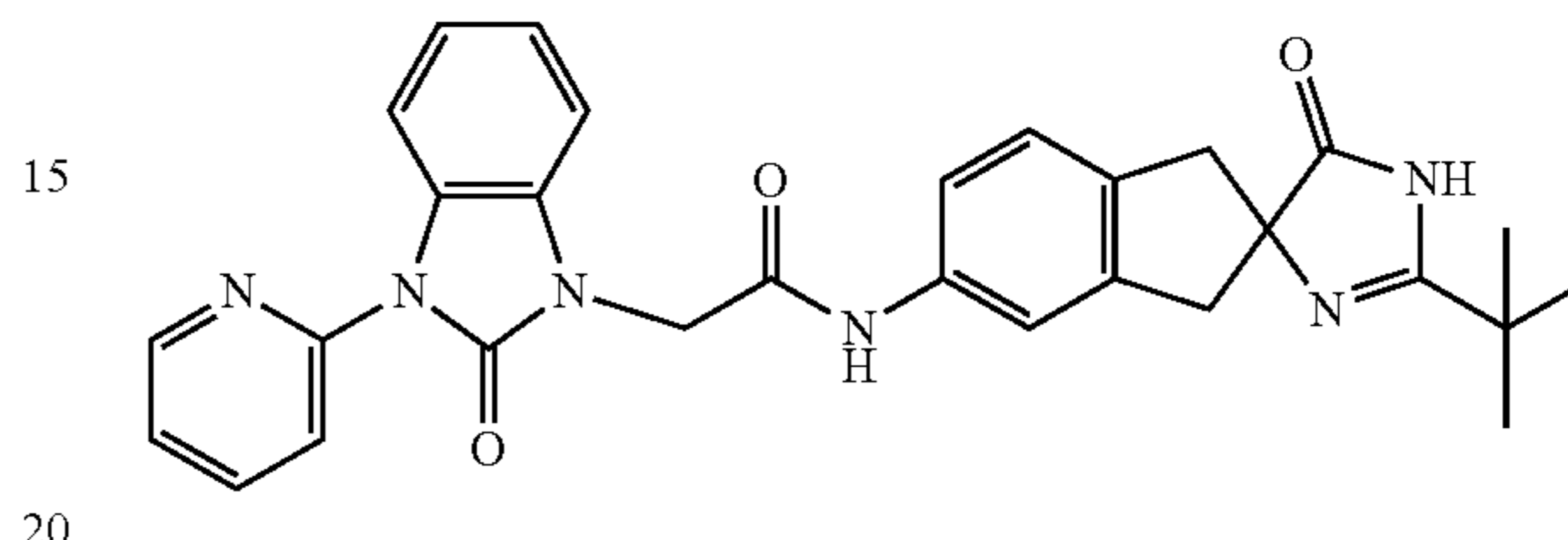
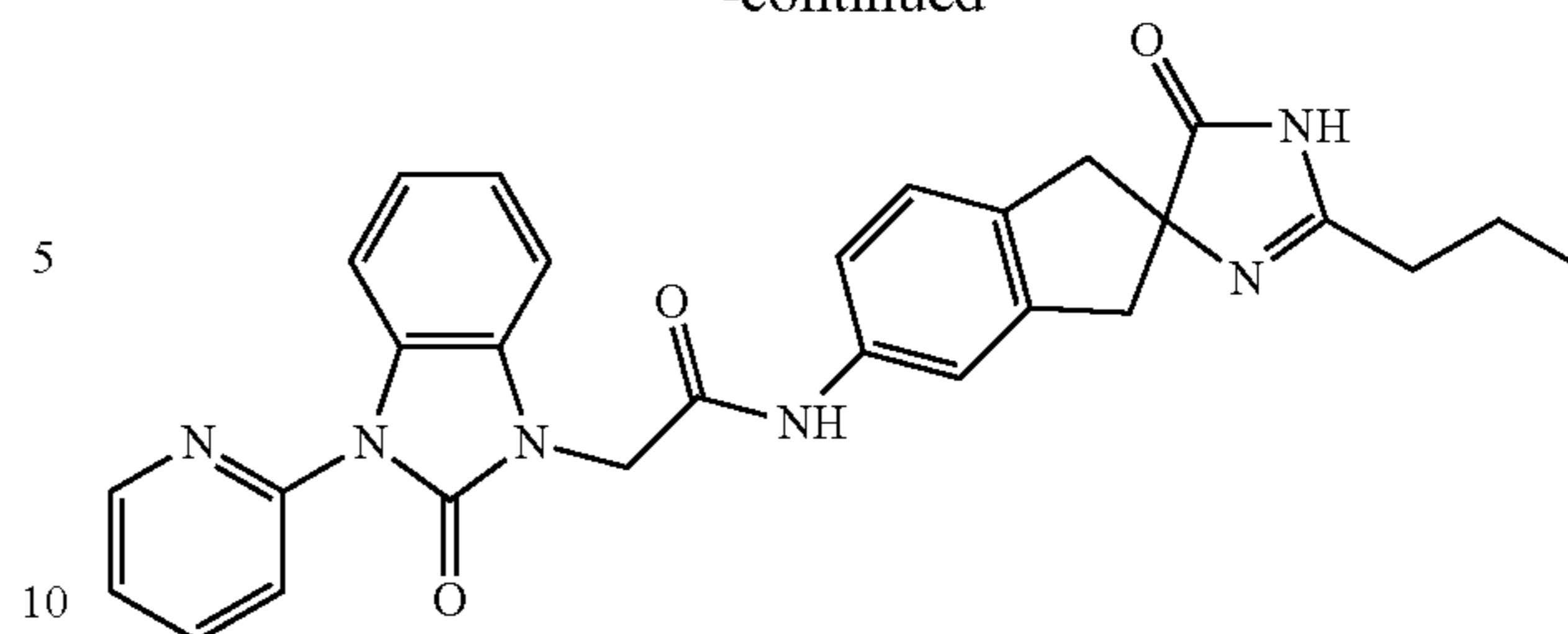
7. A compound of any of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl or pyridyl.

8. A compound of claim 1, which is selected from the group consisting of



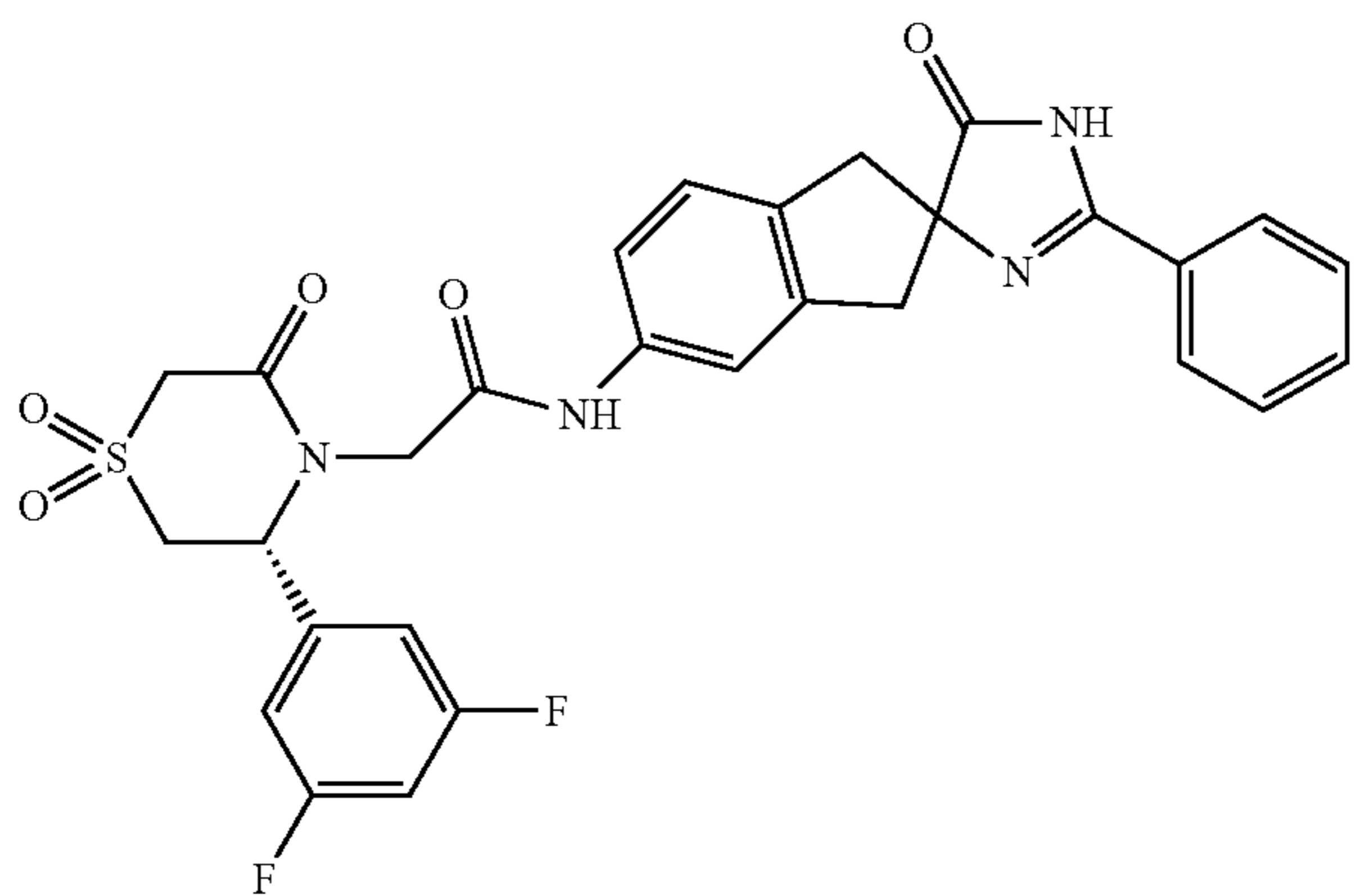
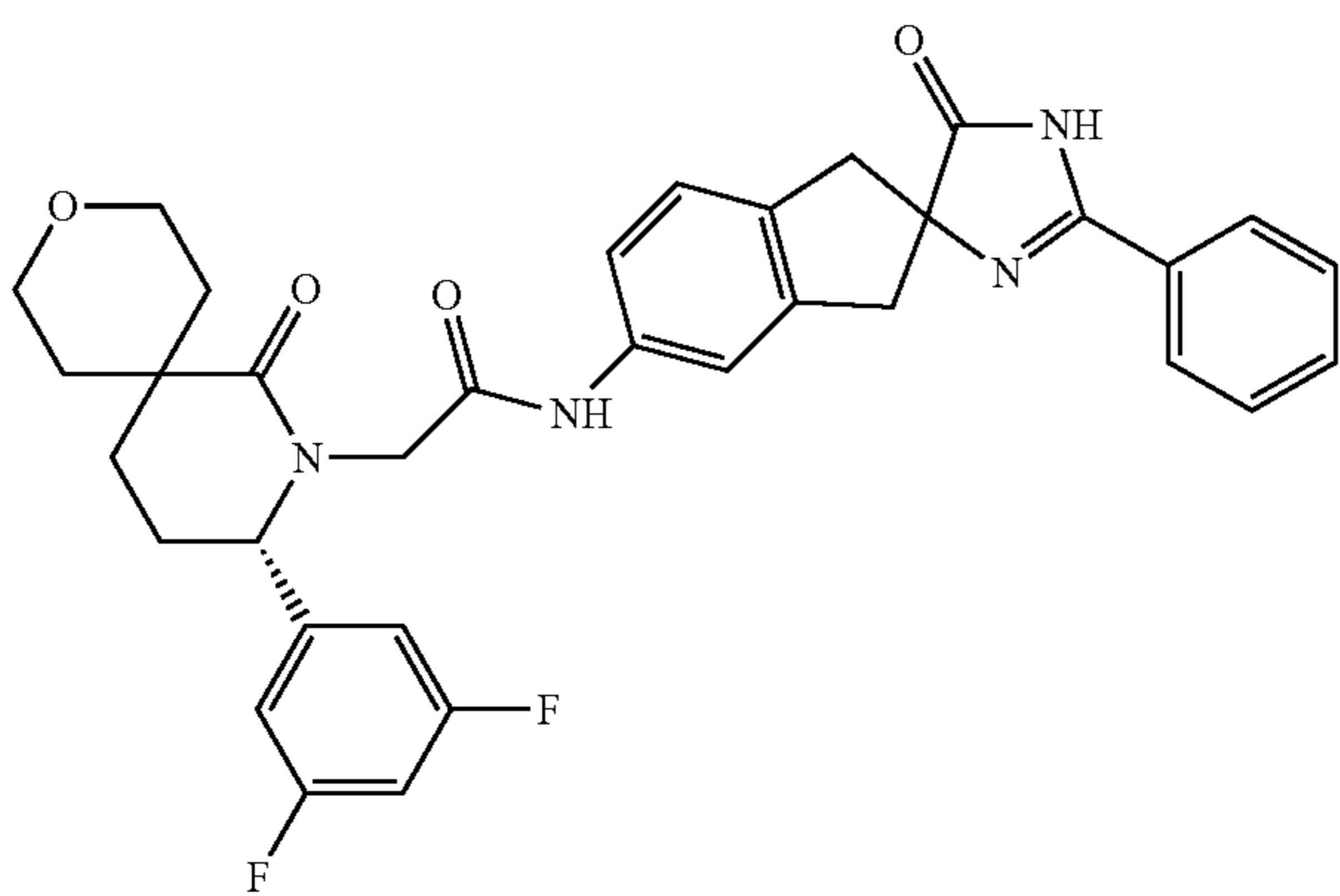
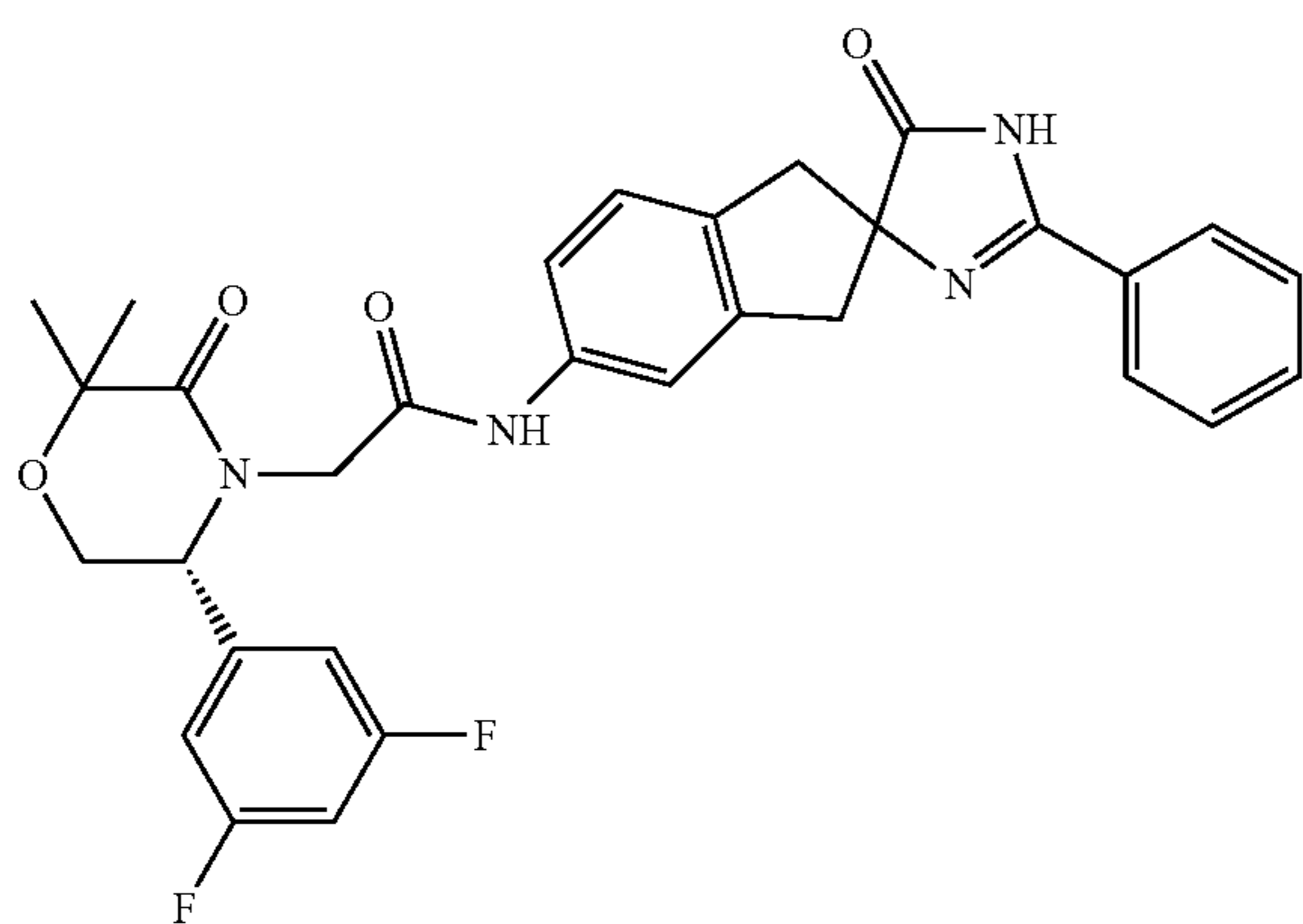
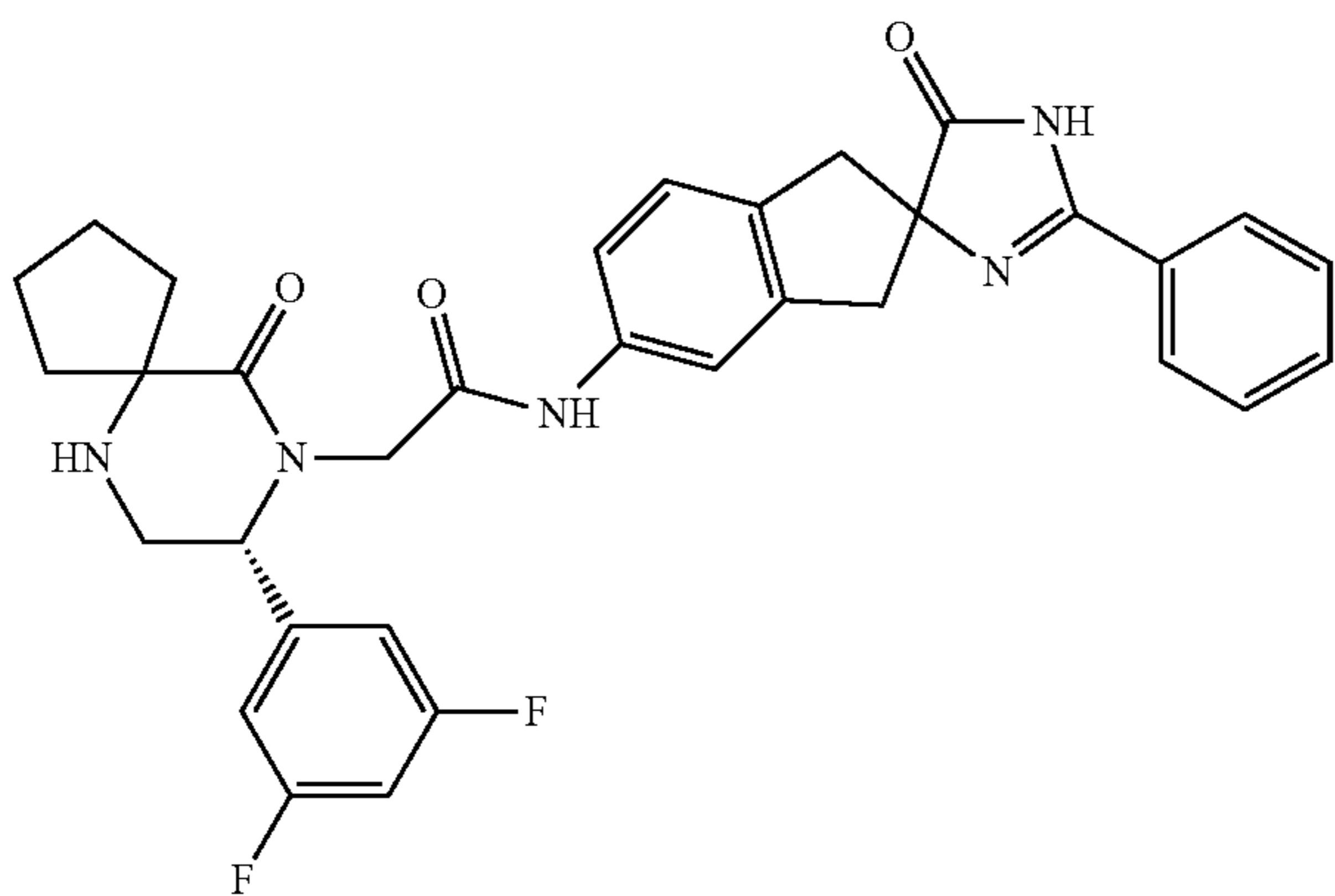
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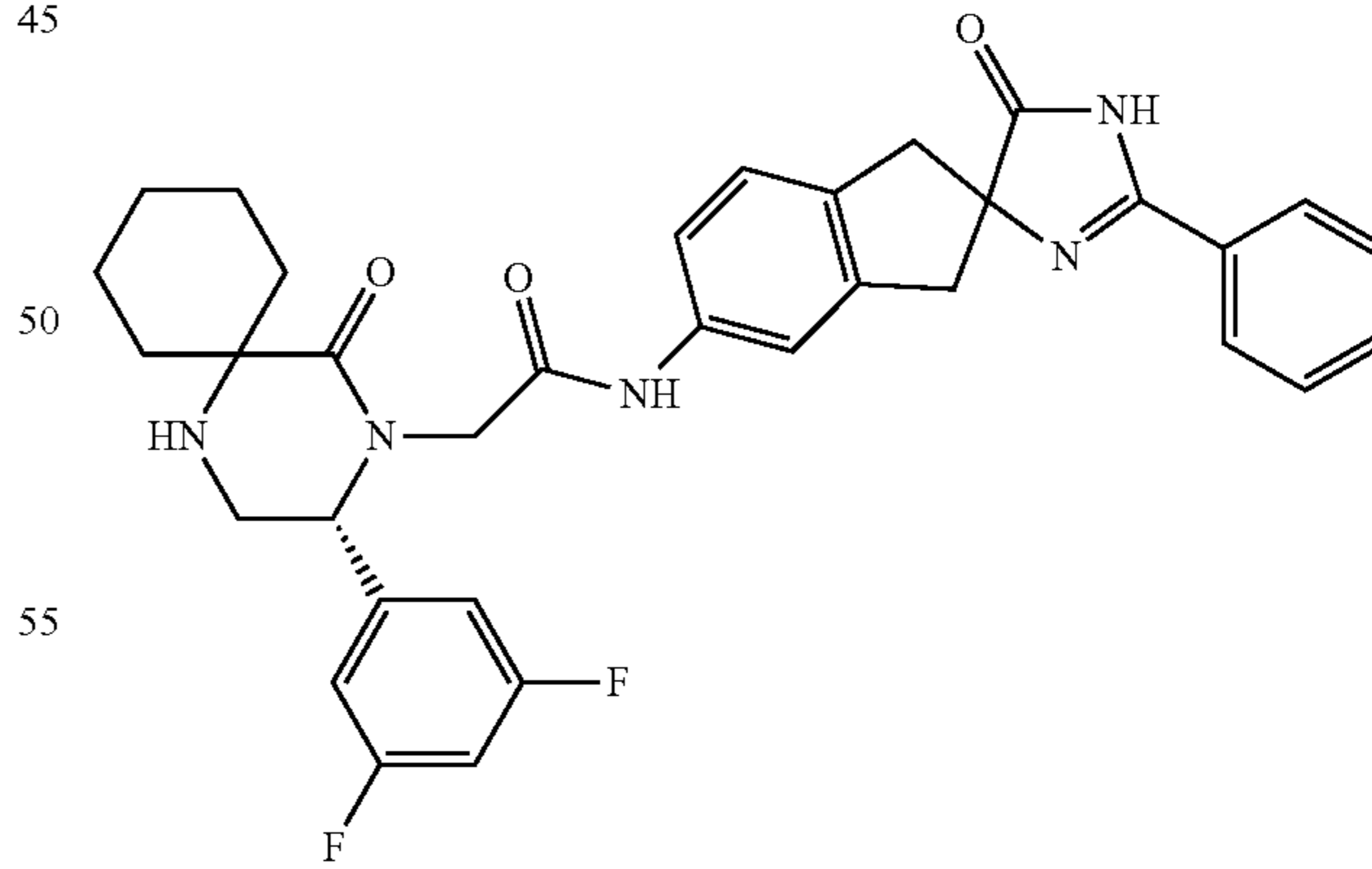
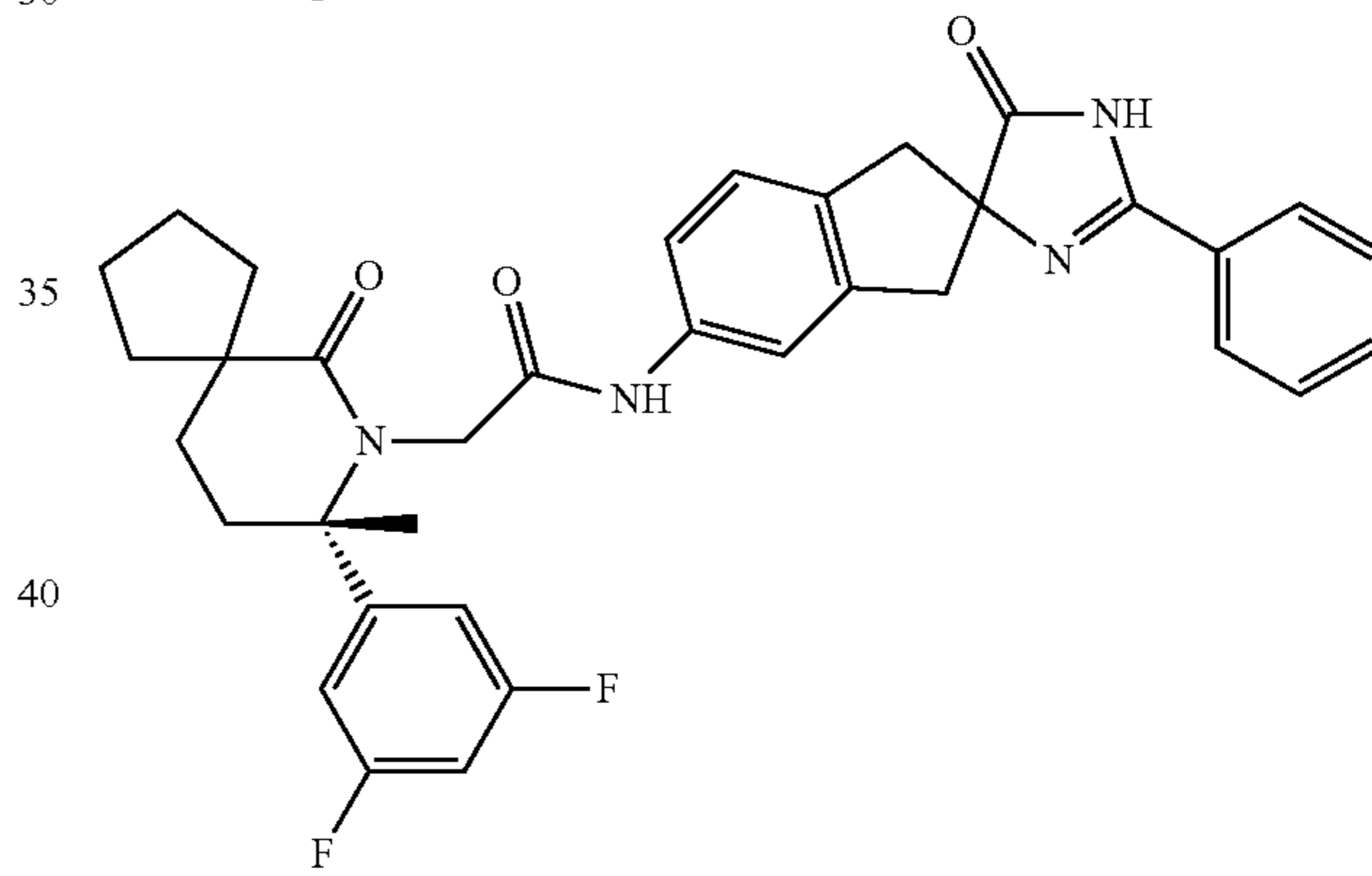
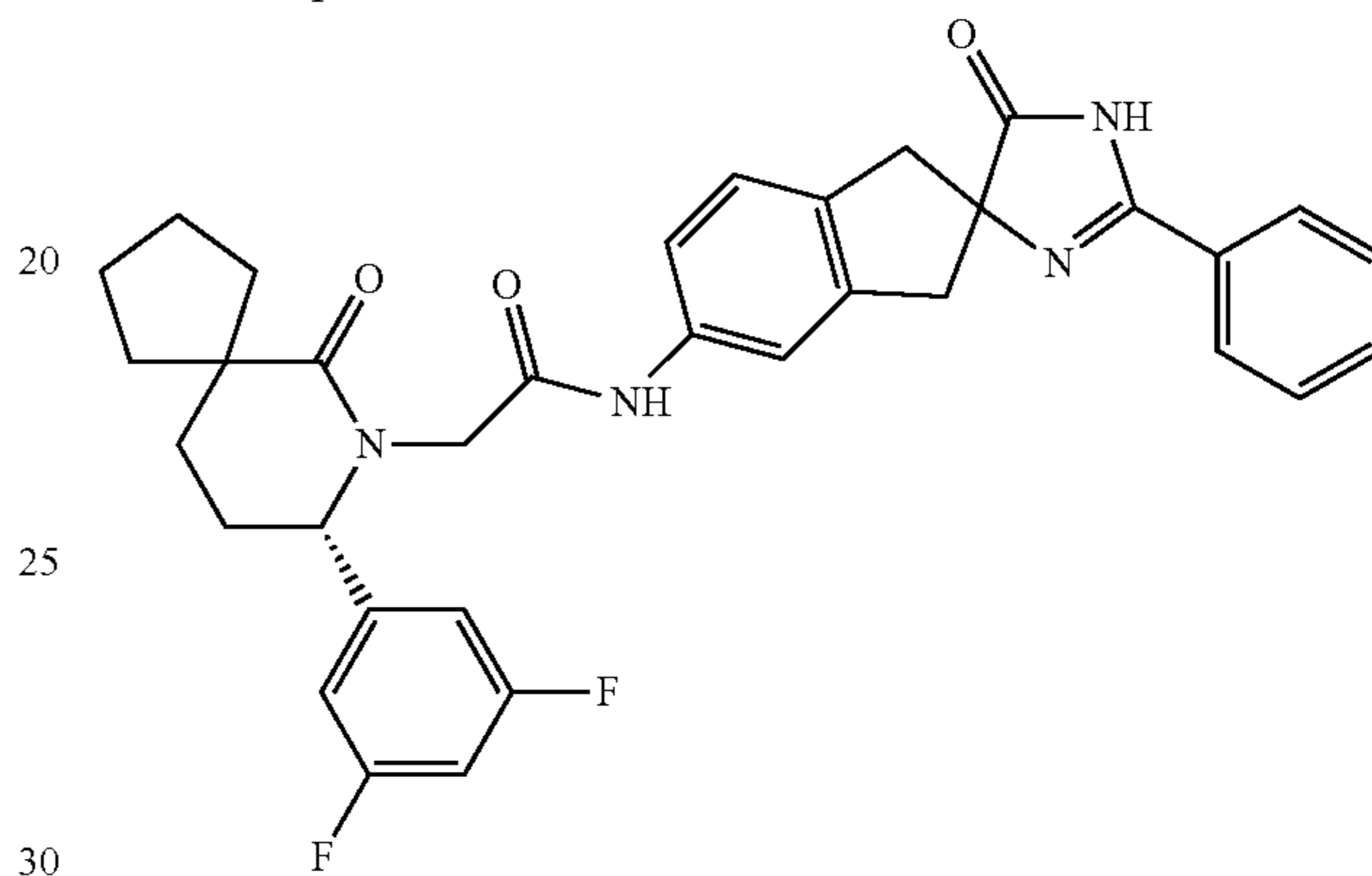
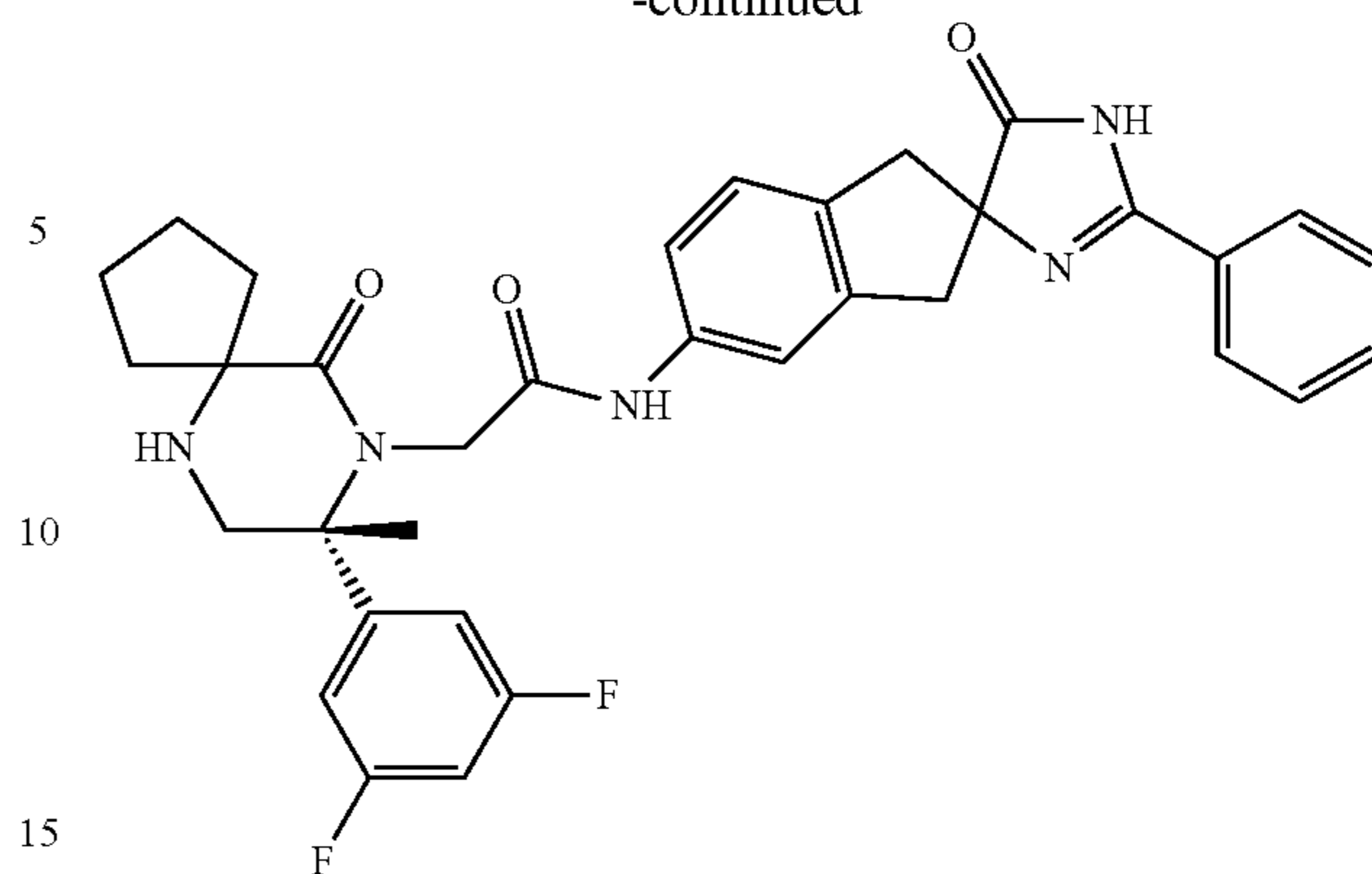
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or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of claim 1, or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,569,291 B2
APPLICATION NO. : 13/119534
DATED : October 29, 2013
INVENTOR(S) : Craig A. Stump

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 189 days.

Signed and Sealed this
Twenty-third Day of May, 2017



Michelle K. Lee
Director of the United States Patent and Trademark Office